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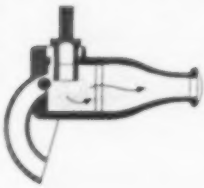

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1. Deuel, H. J., Jr.: Newer Concepts of the Role of Fats and of the Essential Fatty Acids in the Diet, Food Res. 20:81 (Jan.-Feb.) 1955.

2. Meng, H.C.: Preparation, Utilization, and Importance of Neutral Fat Emulsion in Intravenous Alimentation, in Najjar, V.A.: Fat Metabolism, Baltimore, The Johns Hopkins Press, 1954, pp. 69-92.

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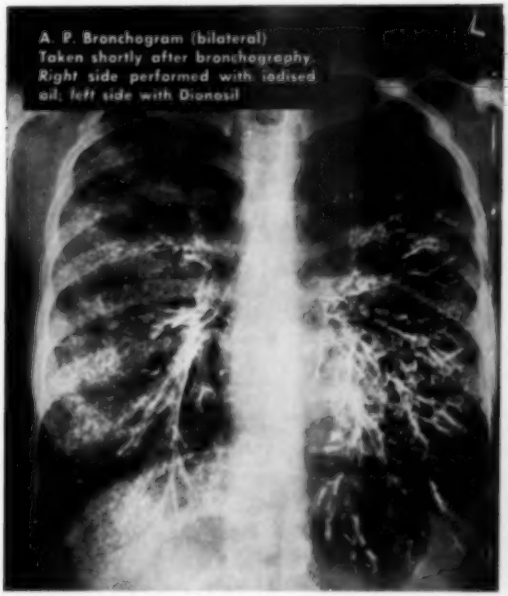
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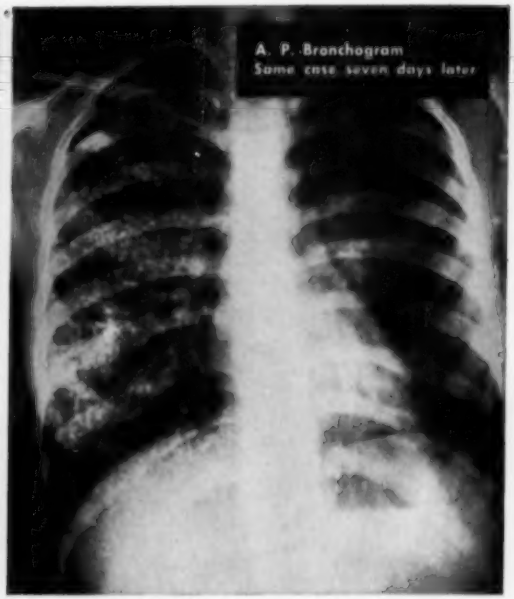

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THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES

VOLUME 73 *February, 1956* NUMBER 2

TUBERCULOSIS STUDIES IN MUSCOGEE COUNTY, GEORGIA[1]

V. Tuberculosis Mortality During Seven Years After a Community-Wide Survey

GEORGE W. COMSTOCK

(Received for publication June 3, 1955)

INTRODUCTION

Fast-tempo community-wide roentgenographic surveys were developed with the hope that identification and treatment of many cases of tuberculosis before the onset of disabling symptoms would markedly improve control of tuberculosis in the surveyed community. During the past decade, which has seen considerable emphasis on this case-finding technique, the tuberculosis death rate has fallen at a greater rate than in previous decades, while the reporting of new cases has remained at a high level. The relation of fast-tempo surveys to either of these phenomena is still a moot question, and their effectiveness in helping to bring tuberculosis under control has been most difficult to measure with any degree of reliability.

One way by which the usefulness of a chest roentgenographic survey may be estimated is to study the tuberculosis deaths in a community after the survey. This should be particularly helpful when tuberculosis mortality can be compared among the persons who were and were not examined in the survey, with the former group subdivided into persons with and without evidence of tuberculosis in their survey films. In addition, the supposition is reasonable that tuberculosis mortality among participants and nonparticipants is related to the prevalence of tuberculosis among these groups and, consequently, might have some bearing on the question whether persons with tuberculosis participate in surveys to the same extent as do other members of the population. Similarly, a study of tuberculosis mortality among persons with normal survey films will give some indication of how often surveys should be repeated.

In 1951 such an analysis was made of the tuberculosis deaths in Muscogee County, Georgia, for the three and one-half-year period after a community-wide chest roentgenographic survey (1). The important findings of that study may be briefly summarized as follows:

> Mortality rates for both whites and Negroes decreased but slightly following the survey. Tuberculosis mortality among the surveyed and non-surveyed did not

[1] From the Muscogee County Tuberculosis Study, Department of Public Health, Columbus, Georgia.

appear to be significantly different, leading to the inference that persons with tuberculosis participated in the survey program to approximately the same extent as did the general population. Death rates among persons with normal survey films revealed an unusually wide discrepancy between the two races: for white persons a low rate—approximately 3 per 100,000 population per year; for Negroes a rate thirteen times greater. The first report tentatively concluded that

> "If future studies confirm these findings, it appears that a complete survey in a white population followed by adequate isolation might be so effective that for some time the tuberculosis control program in the community would consist chiefly of the provision of medical care and follow-up services to persons identified as tuberculous in the survey. For Negroes, it would seem that this would not be sufficient."

At the time of the previous analysis, it was recognized that the number of deaths and the length of the follow-up period were not sufficient to allow firm conclusions. In the present paper, the previous study is extended for an additional three and one-half years and the number of deaths has been increased, as shown in table 1. In addition, a number of refinements in the original data have also been made.

TABLE 1

DEATHS FROM TUBERCULOSIS IN MUSCOGEE COUNTY, BY SURVEY STATUS AND RACE, FOR THREE AND ONE-HALF-YEAR PERIODS, JULY 1, 1946, THROUGH JUNE 30, 1953

Survey Status	July 1, 1946–December 31, 1949		January 1, 1950–June 30, 1953	
	White	Negro	White	Negro
Totals	46	80	21	53
Known cases*	13	17	0	2
"Survey positive"	5	13	4	7
"Survey negative"	3	26	2	22
No roentgenogram	16	16	9	11
Newcomers to community	4	6	4	11
Ineligible, in mental hospitals	5	2	2	0

* Death of one white person brought to our attention after previous paper (1) was prepared.

Description of Study Program

The community-wide survey of 1946 and the subsequent follow-up procedures conducted by the Muscogee County Tuberculosis Study have been described elsewhere (1, 2). Three features of this program are pertinent to this presentation: first, the special census of 1946 which made it possible to identify, among the 95,518 residents,[2] those who obtained roentgenograms in the survey and those who did not. The census also allowed the identification of persons moving to Muscogee County subsequent to the 1946 program. Second, the roentgenographic screening during

[2] The original census population was reported (1) as 95,638, but subsequent corrections have reduced this figure to 95,366 persons with stated race, sex, and age. In addition, 152 persons were enumerated for whom race, sex, or age was not stated.

TABLE 2

DEATHS AND DEATH RATES FROM TUBERCULOSIS IN MUSCOGEE COUNTY BY RACE, FOR THREE AND ONE-HALF-YEAR PERIODS, JANUARY 1, 1943, THROUGH JUNE 30, 1953

Periods	Estimated* Population at Mid-Point of Period			Deaths			Average Annual Death Rates per 100,000 Population		
	Total	White	Negro	Total	White	Negro	Total	White	Negro
January 1, 1943, through June 30, 1946	89,251	61,452	27,799	126	45	81	40.3	20.9	83.2
July 1, 1946, through December 31, 1949	105,079	75,547	29,532	126	46	80	34.3	17.4	77.4
January 1, 1950, through June 30, 1953	127,741	96,014	31,727	74	21	53	16.6	6.2	47.7

* Population estimated by straight-line projections from census populations of April 1, 1940, September 1, 1946, and April 1, 1950.

the seven years following the survey was quite extensive, including a second community-wide survey and eight surveys of special groups, in addition to a chest clinic screening program comprising about 20,000 roentgenograms each year. Even more important for a study of tuberculosis mortality was the relationship with hospitals and private physicians which ensured that virtually all suspected cases of tuberculosis came to the attention of the health department. Third, careful attention has been given to the verification of all reported tuberculosis deaths; and to the investigation of all deaths in which tuberculosis might have been involved, as suggested by the data on the death certificate or from the routine matching of the death certificates with the master tuberculosis index.

MATERIALS AND METHODS

Pre-survey and post-survey mortality rates: Tuberculosis mortality in Muscogee County is reported in table 2 for three and one-half-year periods: one before the survey and two following it. Because of the tuberculosis study program, the post-survey mortality rates are thought to be very reliable. It seems likely that tuberculosis mortality for the pre-survey period was somewhat understated, but one cannot be certain of this. From the first to the second period in table 2, the rate of decline in mortality among both races was somewhat less for Muscogee County than for the United States as a whole. From the second to the third period, the rate of decline among whites was greater than the national rate, whereas for the Negroes it was approximately the same. In all periods, the mortality rates for both races were appreciably lower than those for the nation as a whole (3).

Certainly there was no decline in mortality which could be clearly attributed to the 1946 survey program. Whether or not the increased rate of decline noted later is related to the extensive case-finding and treatment program cannot be determined.

Mortality among participants and non-participants of the survey: One of the unanswered questions about mass surveys is whether the prevalence of unknown tuberculosis is different among those who do and those who do not participate in the program. It seems reasonable to suppose that subsequent mortality rates in the two groups would shed light on this question. For such a comparison to be valid, a number of factors must be considered.

First, in this study, it is possible to identify with considerable certainty the members of the community who had had roentgenograms and those who had not. This was done by matching the survey records of May and June, 1946, against the records for the special population census of September 1, 1946. In the original study (1), all persons who gave

TABLE 3

DEATHS AND DEATH RATES FROM TUBERCULOSIS IN MUSCOGEE COUNTY AMONG PERSONS WHO HAD HAD CHEST ROENTGENOGRAMS IN 1946 SURVEY, BY RACE, JULY 1, 1946, THROUGH JUNE 30, 1953

1946 Survey Status	Population			Observed Deaths			Adjusted* Avererage Annual Death Rates per 100,000 Population		
	Total	White	Negro	Total	White	Negro	Total	White	Negro
Those who had obtained roentgenograms	38,190	22,608	15,582	82	14	68	24.4	7.8	63.0
Those who had not obtained roentgenograms	57,176	44,167	13,009	52	25	27	22.3	10.4	49.9

* The rates for both groups were adjusted to the race-sex-age composition of the 1946 census population of Muscogee County; a further correction was also made by utilizing the population living in the county on January 1, 1950, who had had chest survey films and the population who had not, as estimated from a 2 per cent sample of the 1946 census population on April 1, 1954.

Muscogee County addresses on their survey records were classified as county residents. It now seems more consistent with other publications from this study to utilize the population as given by the 1946 census, and this has been done in the present paper. This change accounts for the population differences in the two publications.

Next, it is necessary to exclude from both groups persons who were under treatment or active follow-up for tuberculosis at the time of the survey and who died later. These "known cases," defined as those in the working case register of the health department at the beginning of the survey program, have been removed from both groups on the same basis as in the previous analysis.

Further, it is well recognized that age, race, and sex have an important relationship to both tuberculosis prevalence and mortality. In the present study, it was believed that a sufficient number of deaths had occurred in both groups, those who had had chest films and those who had not, to allow an adjustment for these factors.

A final difficulty still arose because some deaths might have occurred among residents of the county in 1946 who later moved from the study area. Although the tuberculosis deaths among emigrants are unknown, some information is available concerning the rate of emigration. The whereabouts on April 1, 1954, of a randomly selected 2 per cent sample of the census population was carefully investigated. From this sample, estimates were made of the population, those who had been filmed and those who had not, who were living in the county on January 1, 1950, the mid-point of this study, and these estimates were used in computing the adjusted rates. Consequently, three assumptions have been made: first, that the 2 per cent sample is reasonably representative of the filmed and non-filmed population in regard to emigration and total mortality; second, that the tuberculosis death rates among persons not living in the county at present would be the same as for similar age-race-sex groups still residing here; and lastly, that the rates of emigration and of total mortality were constant for each age-race-sex group throughout the seven-year study period.

OBSERVATIONS

The pertinent data from the present study for estimating the difference in subsequent tuberculosis mortality between the portions of the population who had had chest films and those who had not are given in table 3. For both races, excluding those known to have had tuberculosis before the survey, the adjusted

TABLE 4

DEATHS AND DEATH RATES FROM TUBERCULOSIS AMONG SELECTED GROUPS OF THE RESIDENTS OF MUSCOGEE COUNTY WHO HAD HAD SURVEY FILMS, JULY 1, 1946, THROUGH JUNE 30, 1953

Roentgenographic Status and Race	Population	Deaths	Average Annual Death Rate per 100,000 Population
Positive*			
White	379	9	339.2
Negro	192	20	1,488.1
Negative			
White	22,229	5	3.2
Negro	15,390	48	44.6

* Persons classified as "positive" are those with 1946 survey films read as tuberculosis or suspected tuberculosis by one or both survey film readers, and still considered as tuberculosis or suspected tuberculosis on a subsequent independent review after a six-year follow-up study.

average annual tuberculosis mortality rates during the seven-year period following the survey were 24 per 100,000 among Muscogee County residents who had a survey film and 22 per 100,000 for those who did not have a survey film. For whites, the rates were 8 and 10; and for Negroes, 63 and 50, respectively.

It seems likely that persons who had had survey films should, as a group, have had their tuberculosis detected at a stage more favorable for treatment than those who were not examined. Consequently, in so far as medical treatment may reduce subsequent mortality, one would expect a lower mortality among those who had had chest films than among those who had not. But, in spite of this expectation, the mortality rates for whites were essentially the same in both groups, whereas Negroes with subsequently fatal tuberculosis were more concentrated among the surveyed population. Whatever the explanation for these findings may be, they lend no support to the hypothesis frequently advanced that persons who have reason to believe they may have tuberculosis tend to avoid participation in chest roentgenographic surveys.

Special tuberculosis death rates: One of the most striking findings of the previous analysis was the racial difference in tuberculosis mortality among the groups designated as survey "positives" and "negatives." A refinement has been made in the data since the earlier publication. The populations for the "survey positives" are limited to those considered to have evidence suggestive of pulmonary tuberculosis based on an independent review of the films and clinical data obtained after six years of follow-up study (2). Although this makes the rates more accurate, the resultant changes from the first report are slight.

A comparison of the death rates among whites and Negroes with "positive" and "negative" survey films is made possible by the data in table 4. Again, the mortality rates for "survey positive" cases are rather high: 340 per 100,000 for whites and 1,490 for Negroes. In other words, approximately 2.5 per cent of the whites and 10 per cent of the Negroes with evidence of tuberculosis in their sur-

TABLE 5

DEATHS FROM TUBERCULOSIS AMONG RESIDENTS OF MUSCOGEE COUNTY CONSIDERED TO BE INELIGIBLE FOR THE 1946 SURVEY, BY RACE, JULY 1, 1946, THROUGH JUNE 30, 1953

Groups Considered Ineligible for 1946 Survey	Total	White	Negro
Total	66	28	38
Known cases	32	13	19
In mental hospitals	9	7	2
Newcomers to community	25	8	17

vey films have already died of tuberculosis. Although it may be argued that these fatality rates would have been higher without the survey, it is obvious that tuberculosis is a serious disease even when discovered by examining an ambulant and largely asymptomatic population.

Among the population with normal survey films, the mortality rate for whites still remains low: 3 per 100,000 persons per year. This finding indicates that fatal tuberculosis was uncommon during the next seven years among white persons whose survey chest films were read as normal by two competent examiners. The rate did not decrease during the second three and one-half years of observation, whereas the total tuberculosis mortality rate in white persons fell perceptibly. The numbers are small, however, and chance alone could well have accounted for the failure to observe a proportionate decrease in the rates among the "survey negatives." In any event, a death rate as low as 3 per 100,000 may be interpreted to indicate that tuberculosis has been brought under a fair degree of control among this group in so far as fatal disease is concerned.

In striking contrast, the Negro rate is 45 per 100,000 persons per year for "survey negatives," fifteen times that of the white "survey negatives," and essentially the same as that for the general Negro population in the last three and one-half years of the study period. This is strong evidence that a single survey of a Negro population, even when followed by an intensive tuberculosis control program aimed primarily at the cases discovered in the survey, is not sufficient to bring the disease under control.

Deaths among persons ineligible for the survey: An appreciable number of tuberculosis deaths in the seven-year period occurred among persons classified as ineligible for the 1946 survey, as shown in table 5. Of these, 32 have been defined as "known cases" and, although some of them obtained roentgenograms in the survey, they have been excluded from parts of the analysis for reasons mentioned earlier. Nine deaths occurred among persons who were patients in mental hospitals at the time of the survey. All but one of these persons died while still hospitalized.

In-migration, especially in urban areas, might be expected to account for an appreciable portion of the tuberculosis problem. In Muscogee County, 25 deaths occurred among persons who were not living in the area in 1946. These deaths

account for one-eighth of the total tuberculosis deaths in the seven-year period. The fact that more deaths occurred among Negro newcomers to the community than among whites, in spite of a much greater increase in the white population during this period, suggests that surveys are needed more often among Negroes than among whites.

SUMMARY

An analysis of the deaths from tuberculosis in Muscogee County, Georgia, is reported for the seven-year period following a community-wide survey. Because the population of this county can be subdivided accurately into several groups defined by the survey, a number of observations pertaining to the usefulness of roentgenographic surveys can be made.

(*1*) There is no indication from the mortality data that persons with tuberculosis tended to avoid participation in the survey.

(*2*) The mortality rates were high for persons with evidence of tuberculosis in their survey films. Approximately 2.5 per cent of the whites and 10 per cent of the Negroes so classified died from tuberculosis in this seven-year period.

(*3*) The mortality rate for whites with survey films which showed no evidence of tuberculosis was low: 3 per 100,000 persons per year. For Negroes, the rate was 45, or fifteen times as high.

(*4*) Deaths among persons who moved into the county after the survey was completed accounted for one-eighth of the total deaths from tuberculosis, with the rate for Negroes apparently higher than for whites.

These observations lead to the conclusion that a complete roentgenographic survey of a white population followed by adequate isolation of the infectious cases could reduce the tuberculosis control program, for several years at least, to the provision of medical care and follow-up services for persons identified in the survey as tuberculous. For a Negro population, it appears that case-finding programs should be repeated more frequently.

SUMMARIO

Estudio de la Tuberculosis en el Condado Muscogee, Georgia. V. Mortalidad Tuberculosa Durante Siete Años Después de una Encuesta Colectiva

Preséntase un análisis de las muertes por tuberculosis en el Condado Muscogee, Georgia, durante el septenio consecutivo a una encuesta que comprendió toda la colectividad. Por poderse subdividir la población de este condado exactamente en varios grupos definidos en la encuesta, cabe hacer varias observaciones relativas a la utilidad de las encuestas radiográficas,

(*1*) No arrojan indicación alguna los datos de mortalidad de que los tuberculosos tendieran a evitar participación en la encuesta.

(*2*) Las tasas de mortalidad fueron altas para las personas que mostraban signos de tuberculosis en las radiografías de la encuesta. Approximadamente 2.5 por ciento de los sujetos de raza blanca y 10 por ciento de los de raza negra así clasificados fallecieron de tuberculosis en dicho septenio.

(*3*) Las tasas de mortalidad para los blancos cuyas radiografías resultaron normales en la encuesta fueron bajas: 3 por 100,000 personas por año. Para los sujetos de raza negra, la tasa fué de 45, o sea quince veces más alta.

(4) Las muertes entre personas que se mudaron al condado después de terminar la encuesta representaron la octava parte de la mortalidad total por tuberculosis, siendo el coeficiente para los sujetos de raza negra aparentemente más alto que para los de raza blanca.

Estas observaciones conducen a la conclusión de que una encuesta radiográfica completa en una población de raza blanca, seguida del aislamiento adecuado de los casos infecciosos, podría reducir el plan de lucha antituberculosa, a lo menos durante varios años, al suministro de asistencia médica y servicios de observación para las personas identificadas como tuberculosas en la encuesta. Para la población de raza negra, parece que deben repetirse con mayor frecuencia las obras de descubrimiento de casos.

RESUME

Etudes sur la tuberculose dans le Muscogee County, Georgia. V. Mortalité tuberculeuse pendant sept années après une enquête municipale

Une analyse des décès par la tuberculose dans le Muscogee County, Georgia, est rapportée, elle couvre une période de sept années succédant à une enquête à l'échelle municipale. La population de ce comté pouvant être subdivisée avec précision en plusieurs groupes définis par l'enquête, un certain nombre d'observations relatives à l'utilité des enquêtes radiologiques peuvent être faites.

(*1*) Il n'y a pas d'indication, d'après les données de mortalité, que les individus atteints de tuberculose aient essayé d'éviter la participation à l'enquête.

(*2*) Les taux de mortalité étaient élevés pour les individus présentant des signes de tuberculose dans leurs clichés de dépistage. Approximativement 2,5% des sujets de race blanche et 10% des sujets de race Noire sont morts de tuberculose dans cette période de sept ans.

(*3*) Le taux de mortalité pour les blancs dont les films de dépistage étaient normaux était faible, 3 pour 100.000 hommes-année. Pour les Noirs, le taux était 45 pour 100.000 hommes-année, soit quinze fois plus élevé.

(*4*) Les décès, parmi les individus qui se sont installés dans le comté après la fin de l'enquête, représentaient un huitième de la totalité des décès par tuberculose; le taux pour les Noirs étant plus élevé que pour les blancs.

Ces observations mènent à la conclusion qu'une enquête radiologique complète d'une population blanche, suivie par l'isolement adéquat des cas contagieux, pourrait, pour plusieurs années au moins, réduire le programme antituberculeux, à assurer les soins médicaux et les services de surveillance aux cas de tuberculose enregistrés dans l'enquêtede dépistage. Pour la population noire, il apparaît que les programmes de dépistage systématique devraient être répétés plus fréquemment.

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THE PRESENT STATUS OF PULMONARY RESECTION IN THE TREATMENT OF LOCALIZED NECROTIC RESIDUALS OF PULMONARY TUBERCULOSIS[1]

A Review

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INTRODUCTION

The advent of chemotherapy in 1946 has changed and continues to change many of our long-established concepts in the treatment of pulmonary tuberculosis. This applies particularly to minimal lesions or to well-localized cavitary lesions with minimal parenchymal involvement. The management problem of the residual necrotic lesion after prolonged chemotherapy is more and more pertinent and at present is the subject of seemingly endless debate. In the modern era of effective chemotherapy, temporary collapse measures are little used, nor are they necessary, and surgical resection is an increasingly essential feature of any well-integrated definitive treatment plan for such patients.

The essence of the problem concerns the viability of the morphologically normal tubercle bacilli found in nearly all residual lesions, the basic pathology of such lesions, and their response to chemotherapy. Ultimately the problem is concerned with the safe selection of those patients suitable for long-term chemotherapy alone or long-term chemotherapy accompanied by resection. Cavitary residuals are surgical problems and are not treated by drugs alone in patients with operable lesions. Modern antituberculosis drugs properly administered are so effective that the late follow-up results will probably show only a small percentage difference in relapse rates between the patients who received long-term chemotherapy alone and those who underwent resection for noncavitary residuals in addition to the prolonged chemotherapy. In short-term follow-up studies, however, more favorable results have been observed in general in the resected patients with respect to relapse.

The writers wish to present their current concepts of the management of this difficult and controversial group of patients. It is fully realized that modifications in treatment and in the type of case selected may be necessary as more information becomes available concerning the ultimate behavior of localized necrotic residuals of pulmonary tuberculosis following prolonged antimicrobial therapy.

INITIAL PATIENT EVALUATION IN PULMONARY TUBERCULOSIS

In this hospital, the initial patient evaluation is made by history, physical examination, and by roentgenographic and other laboratory studies. As effective

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TABLE 1

THE DEFINITIVE TREATMENT OF ACTIVE PULMONARY TUBERCULOSIS BASED ON AN ESTIMATE OF THE LUNG PATHOLOGY

Classification of Lesions	Medical Treatment: Specific Drugs* Temporary Collapse	Surgical Treatment: Pulmonary Resection and/or Thoracoplasty
1. Unclassified lesions (new patients)	Start therapy on tentative classification; use response to drugs for final plans.	
Reversible Disease		
2. Acute miliary tuberculosis 3. Chronic disseminated nodular tuberculosis 4. Diffuse exudative tuberculosis	Reversible lesions are medical problems. Use continuous drug therapy until the inactive stage of disease. Operative procedures are not required.	
Irreversible—Poorly Resolving Disease, Acute or Chronic		
5. Acute caseous pneumonic tuberculosis	Medical measures (drugs and possibly pneumoperitoneum) are required for early phase of treatment and may prove definitive.	Surgery is considered after six to twelve months of drug therapy for residual necrotic lesions and cavitary lesions
6. Chronic fibrocaseous tuberculosis (caseonodose and fibrocavitary lesions)		Old irreversible lesions are primarily surgical problems. Operate promptly when required and continue chemotherapy six to twelve months after surgery.
Mixed Reversible and Irreversible Lesions, Acute and Chronic, Mixed		
7. Mixed lesions Reversible exudative component: considered first Irreversible fibrocaseous component	Treat as a medical problem with chemotherapy and possible pneumoperitoneum.	If not controlled by medical management, surgery will be required for definitive therapy.

* Chemotherapy is used for all lesions to at least the stage of "inactive disease," determined by 1950 National Tuberculosis Association classification.

therapy is now available for most pulmonary tuberculosis patients, the phthisiologist and thoracic surgeon must assess the over-all problem presented by an individual patient and the treatment potentials of his particular lesion.

To plan effective treatment, studies must be initiated on the patient's admission to the hospital to determine as accurately as possible the following points:

The probable age or duration of the disease process. Is the lesion new, old, or mixed?

Does the lesion suggest resolving reversible pulmonary infiltration?

How much probable destruction of lung tissue has occurred? An attempt is made to decide the location of the involved area and the presence of probable necrosis or obvious cavitation.

The extent of disease is estimated.

The presence of extrapulmonary involvement such as bronchial or pleural disease is determined.

The prime consideration in this initial assessment of the patient's problem is to arrive at a clinico-pathologic evaluation of the patient's lesion. This estimate of the disease process and possible treatment response is the tentative starting point of therapy for each patient.

Tempel and Forsee (1) have presented a very useful clinico-pathologic classification in use at Fitzsimons Army Hospital (table 1). The value of this tentative classification of the patient's pathologic lesion and the potential response to treatment increases as the clinician improves his own acumen by constant correlation of his initial clinical impression and the actual tissue changes present in specimens from patients who eventually are treated with surgical resection.

PATHOLOGY

The most minute focus of pulmonary tuberculosis is essentially a necrotizing pneumonitis. The actual amount and extent of tissue necrosis varies widely in the individual patient as does the healing process in terms of ultimate reliability and stability. This parenchymal focus of tuberculosis may heal by fibrosis, undergo resolution, or caseation necrosis may supervene. In any tuberculous patient all three factors are present in varied degrees. Corylos (2) emphasized in 1933 that occlusion of the draining bronchus was the most essential factor in cavity closure and healing. Auerbach and Green (3), in 1940, studied cavity healing in the pre-drug era and concluded that inspissation of caseous material was the most common mechanism of cavity closure, organization of cavitary contents being less important. In all instances of closed cavities, however, they found that the draining bronchi ended blindly in an area of fibrosis in relation to the cavity wall. Auerbach and co-workers (4) have also studied the behavior of cavities in streptomycin-treated patients. The most prominent feature of such cavities was extensive re-epithelization of the bronchocavitary junction. The lumen of the cavity decreased and the caseous contents inspissated. Rarely, as described by Pagel and Simmonds (5), open cavity healing may occur. Necrotic debris is discharged and the cavitary wall is lined by epithelium which originates in the draining bronchus. The cavity is thus converted into a part of the bronchial system.

Pathologic study affords a key to the behavior of the residual necrotic tuberculous lesion and is the only logical basis for gradually formulating an ideal treatment program. Such a study at present affords certain definite answers but offers an incomplete explanation for other observed characteristics of these necrotic residuals. Certain pathologic facts come to mind from the study of these lesions.

Pulmonary tuberculosis is a destructive lesion and one must estimate as accurately as possible the degree of parenchymal destruction in the individual case to formulate a treatment program. The most effective antimicrobial therapy obviously cannot remake irreversibly destroyed lung parenchyma.

With streptomycin therapy, tuberculous cavities frequently decrease in size or disappear from view in conventional roentgenograms. Pathologically, in drug-treated patients, tuberculous cavities do not seem to close with much greater frequency than in untreated cases. In view of this pathologic fact, the standard roentgenograms alone are inadequate. Eccentric views and tomograms frequently demonstrate residual areas of cavitation or radiolucence confirmed in the pathologic specimens.

Re-epithelization of the bronchocavitary junction extending in varied degrees along the cavitary wall should make it more difficult to sterilize a tuberculous cavity under chemotherapy, as the bronchus is open and the tubercle bacillus is an aerobic organism.

Pathologists frequently comment that more filled tuberculous cavities are observed during multiple-drug intermittent therapy. This fact is hard to correlate with Auerbach's (4) observations of the patent bronchocavitary junction.

Liquefaction of residual necrotic lesions may occur unpredictably. Rich (6) has pointed out that neutrophils are usually present in the cavitary contents and freshly softened caseous material contains many tubercle bacilli. It is hard to understand why all such lesions, except those with extremely thick fibrous encapsulations, do not liquefy and discharge their contents.

The size of a necrotic focus is not all important. No one knows how large a necrotic focus may reliably be encapsulated. Since liquefaction may occur unpredictably, the size of the focus is therefore important, as invariably the larger the lesion the larger the draining bronchus and the greater the opportunity for easy bronchial dissemination.

Large caseous foci, under the influence of chemotherapy, may seem very indolent pathologically. On the other hand, minute lesions may be extremely active pathologically and offer a real hazard of future relapse. The factor of individual variation in healing enters as, from the pathologic standpoint, a lesion of the same size may show reliable or precarious healing in an individual patient under the influence of the same rest regimen and chemotherapy program.

Visible tuberculous endobronchial disease of major bronchi responds very well to multiple-drug therapy. Pathologically, the frequency and extent of subsegmental tuberculous endobronchial disease, even after long-term chemotherapy, suggest a difference in the healing process in the smaller segmental and subsegmental bronchi. Olson and associates (7) found a 27 per cent incidence of endobronchial tuberculosis in specimens from patients (cavity never demonstrated) who received streptomycin-PAS for nine months or more.

Some of the pertinent pathologic aspects in the study of residual necrotic tuberculous lesions after long-term chemotherapy have been considered above. Certain points appear contradictory at this time, due to our incomplete knowledge. All agree, however, that such pathologic study is the key to the future in the sense that only by this means can lesions ultimately be sorted into groups which possess certain common features which would indicate either the safety of long-term chemotherapy alone or the need for additional treatment in the form of resection of the arrested lesion. Continued pathologic study of treatment

response should lead to methods for the selection of therapy with a minimal risk of relapse for the individual patient.

BACTERIOLOGY

In 1948, D'Esopo, Ryan, and Medlar (8) attempted to determine whether para-aminosalicylic acid (PAS) given with streptomycin over a prolonged period significantly altered the susceptibility of tubercle bacilli to streptomycin. Under long-term chemotherapy with streptomycin-PAS, however, their patients attained a state in which cavities were closed, the sputum was noninfectious, and the roentgenographic findings were stable (9).

Medlar (8, 10, 11) suggested that such lesions should be resected since they were necrotic residual foci. This was done on a large scale. The presence of necrosis and large numbers of acid-fast bacilli was demonstrated but the microorganisms were nonculturable. A tremendous amount of investigative work has been done since this time, but the fundamental problem still remains of attempting to correlate the bacteriology and pathology of such resected residual necrotic lesions. Since the elements for relapse are present, namely, tubercle bacilli, a communicating bronchus, and caseation necrosis, the question of the viability of these microorganisms becomes extremely important.

The question revolves around the problem of determining whether tubercle bacilli in such lesions are alive, dead, or dormant, but revivable and potentially dangerous. D'Esopo (12) pointed out that, when patients receive streptomycin-PAS (the streptomycin twice weekly) for at least eight months and the lesion is then resected, 25 per cent of the lesions will be positive for acid-fast bacilli on microscopy but only 10 per cent by culture. After eight months, however, in the patient treated with daily streptomycin-PAS, no resected lesion will yield cultural tubercle bacilli. Hobby (12) reviewed the combined data of six Veterans Administration hospitals. Five hundred and fifteen resections were reported. Of six hundred and sixty-one necrotic closed cavities, eighty-five (12.8 per cent) were positive for tubercle bacilli by culture and/or guinea pig inoculation. Of twenty-three apparently open cavities, 70 per cent were positive on microscopy and 74 per cent by culture or guinea pig inoculation. Recently, however, Hobby and associates (13) have reported a very interesting study utilizing long-term incubation *in vitro* of specimens from patients treated with bi-weekly streptomycin and daily PAS. This improved technique has definitely demonstrated a much higher percentage of positive cultures even from closed necrotic lesions and offers additional proof that these bacilli are revivable but that our routine culture methods are inadequate.

Dubos (14) has pointed out that tissue cells around a tuberculous lesion accumulate lactic acid locally. He has further emphasized that during necrosis, enzymes release long-chain fatty acids. Such fatty acids are powerful antimycobacterial agents *in vitro* and their effect is even greater in an acid environment. Long-chain fatty acids and lactic acid in low concentrations do become bactericidal to tubercle bacilli when the oxygen tension is low. Semianaerobic conditions probably prevail in these residual necrotic lesions. Dubos questions, however, the

over-all importance of a low oxygen tension in closed lesions and believes that the amount of oxygen in solution in tissue fluids may be sufficient to allow bacilli to survive and perhaps even grow.

D'Esopo (9) believes the organisms to be nonviable. Many of D'Esopo's cases are unique in that the patients are on a daily streptomycin-PAS regimen, and such patients cannot be compared bacteriologically with patients treated with intermittent streptomycin and daily PAS. Dubos (14) considers the organisms to be in a dormant phase, nonculturable, but capable of reviving. Hobby's (13) improved culture techniques and results previously mentioned strongly support Dubos' stand.

If the total population of tubercle bacilli in a closed lesion could be proved to be dead, there would be no necessity for surgical resection of certain localized necrotic residuals except possibly such mechanical changes as might produce essentially nontuberculous complications. The present writers believe that these microorganisms, in the light of present knowledge, must be presumed to be viable or revivable. Evidence of death of the bacilli is certainly of a completely negative type at this point and one cannot merely state that they are dead, but must assume the burden of proof. The ideal situation, of course, would be the utilization of some method such as the Warburg apparatus, as pointed out by Raffel (12), which might indicate whether the bacilli are still respiring minutely. The consensus in this institution is that prudent consideration at this point demands assumption of viability or potential danger of these microorganisms and that certain lesions, therefore, on pathologic and bacteriologic grounds, require surgical resection as well as long-term chemotherapy.

SURGICAL INDICATIONS

During surgical exploration of residual necrotic lesions which persist after long-term chemotherapy, the severity of the pathologic residuals present is impressive. The necrotic foci are usually much more striking with the lung under palpation than had been anticipated from preoperative roentgenography. Pathologic study of resected specimens usually will amply confirm such findings. Pathologically, there is much more extensive residual disease than would have been expected from the preoperative roentgenographic evaluation alone. A corollary phenomenon is the fact that the original roentgenographic findings at the onset of drug therapy are a much more accurate estimate of the actual surgico-pathologic findings in the patient coming to resection. Thus no patient should be discharged as having attained maximum hospital benefit following prolonged chemotherapy solely on the basis of conventional roentgenograms. Careful studies, including tomograms, should usually be done to exclude residual necrotic lesions of significance often undetectable on the standard roentgenograms. The thoracic surgeon should base his operative decision on the initial pretreatment roentgenograms as well as on the roentgenographic studies during and following prolonged chemotherapy. Careful utilization of preoperative tomographic studies in both the postero-anterior and lateral projections offers an extremely accurate index of surgico-pathologic findings and the studies correlate

very closely with the actual operative findings. They also assist in formulating a surgical decision on the extent of the operative procedure required in the individual patient.

The size of a roentgenographically demonstrated residual lesion is only one factor and certainly not the most important factor in deciding whether the lesion should remain *in situ* or be excised. The type and size of the necrotic focus which may be safely encapsulated under ideal conditions influenced by drug therapy are still unknown. Resection of minute lesions concomitant with excision of a principal lesion often reveals amazingly active pathologic changes in the small, presumably innocuous foci. Liquefaction necrosis in a nodose tuberculous residual lesion certainly occurs, is unpredictable, and is not clearly understood. Individual patient response and individual degree of destructiveness of the caseonecrotic lesion after long-term chemotherapy is likewise very variable. Pathologic study of various types of residuals would appear to be the only logical means of eventually classifying residual lesions into those which are safe for long-term chemotherapy and those with inherent pathologic features of dangerous nature suggesting that resection would give better long-term results and prevent future relapse.

Pathologic specimens contribute a great deal to intelligent planning of the patient's treatment. Important information obtained in this way includes the degree of pathologic activity, demonstration of previously unsuspected lesions, the demonstration of persistent bronchial communications with cavitary lesions, and, frequently, the demonstration of unsuspected bronchial disease. All such observations promote formulation of a rational postoperative treatment plan, particularly in patients with ipsilateral and contralateral residuals remaining *in situ*.

Segmental resection is the procedure of choice for the resection of the residual lesion after prolonged chemotherapy. The inherent pathology of these residual lesions, with the high incidence of extensive active subsegmental endobronchial tuberculosis, make wedge resection potentially hazardous and a procedure to be avoided. Operative mortality and morbidity is a factor of some consideration. In the young, healthy patient, the operative mortality for segmental resection is certainly less than 1 per cent. Postoperative complications are frequent, and there is a high morbidity index. Nevertheless, these factors contributing to morbidity are very nearly incidental findings in the postoperative segmental resection and are rarely severe postoperative complications in the ordinary sense. In any case, in the individual patient one must balance this risk of mortality and morbidity against the risk of future relapse and resultant morbidity from dangerous residual lesions.

SPECIFIC OPERATIVE INDICATIONS

In general, most serious residual necrotic lesions deserve resection in an otherwise healthy patient. One must individualize, however, and, if even a relative medical contraindication exists, surgery may not be indicated. One should not expose the patient to an unusual operative hazard of an immediate nature in

order to prevent a later risk of local relapse. Although the latter may be serious in nature, it certainly does not ordinarily constitute a threat to life. Surgical indications, in terms of resections as the usual procedure or under further study for incorporation as usual procedure at Fitzsimons Army Hospital, are shown in Chart I. The absolute and relative surgical indications revised from Mayock's

CHART I

SURGICAL INDICATIONS AFTER PROLONGED CHEMOTHERAPY

Type of Lesion	Definitive Treatment		
	Resection		Long-Term Drugs
	Usual	Study	
A. Cavitary lesion			
1. Persistent, overt, air-filled	X		
2. Laminographic cavity	X		
3. Inspissated cavity	X	X	X
B. Noncavitary lesion			
1. Old, relapsing, recurrent disease	X		
2. Insignificant disease by roentgenogram; clinical and/or bacteriologic activity manifest	X		
3. Solid caseonodose residual			
More than 3 cm.	X		
Less than 15 mm.		X	X
More than 15 mm.	X	X	
4. Active tuberculous bronchial disease	X		
5. Small localized residuals in area of damaged lung	X	X	

CHART II

SURGICAL INDICATIONS FOR THE RESECTION OF TUBERCULOUS LESIONS APPARENTLY ARRESTED AFTER PROLONGED CHEMOTHERAPY

I. *Absolute*
   - *a*. Air-filled cavity with sputum positive for tubercle bacilli
   - *b*. Nodule (any size) with sputum positive for tubercle bacilli
   - *c*. Bronchial disease with sputum positive for tubercle bacilli
   - *d*. Old relapsing disease—previous adequate chemotherapy
   - *e*. Caseonodose residual more than 3 cm.

II. *Strong*
   - *a*. Air-filled cavity with sputum negative for tubercle bacilli
   - *b*. Inspissated cavity
   - *c*. Caseonodose residual 1.5 to 3 cm.

III. *Moderate*
   - *a*. Caseonodose residual 1 to 1.5 cm.
   - *b*. Small residuals 1 cm. in area of damaged lung
   - *c*. Post-tuberculous bronchiectasis with sputum negative for tubercle bacilli

IV. *No surgical indication*
   - *a*. Caseonodose residuals less than 1 cm.
   - *b*. Linear or placque-like fibrotic residuals
   - *c*. Emphysematous bleb or bulla

CHART III

	Case Number
A. Cavitary lesions	
1) Open cavity—plain roentgenogram	1
2) Open cavity—planigram	2
3) Inspissated cavity with:	
a) Patent bronchocavitary junction	3
b) Bronchostenosis	4
c) Tangential bronchus	5
d) Epithelialized cystic cavity	6
e) Subsegmental endobronchial disease	7
f) Apparently stable residual—subsequent relapse (roentgenographic, clinical, or bacteriologic)	8
B. Noncavitary lesions	
1) Old, chronic, relapsing disease: significant roentgenographic changes	9
2) Clinical and/or bacteriologic activity manifest; insignificant disease by roentgenogram	10
3) Solid caseonodose residual more than 1.5 cm.	11
4) Active tuberculous bronchial disease	12
5) Localized residuals in area of damaged lung	13

(15) original concept are listed in Chart II. Obviously, such divisions of surgical indications are arbitrary to a certain extent and will vary with individual internists and surgeons. Cases illustrated in figures 1 through 13 (placed at the end of the article) have been selected to illustrate pertinent aspects of these controversial lesions in deciding for or against surgery and in understanding better their inherent potential for relapse (Chart III).

DISCUSSION

The minimal lesion of pulmonary tuberculosis in the pre-drug era was certainly not an innocuous focus. Mitchell and Knudsen (16) recently reported the seven-year results for two hundred and eighty-nine cases of minimal tuberculosis in which the treatment consisted of bed rest. The cumulative reactivation rate was 37 per cent. In 25 per cent of these patients, the process progressed beyond the stage of minimal tuberculosis; one-third of the patients had two or more reactivations, and 60 per cent of all reactivations occurred within one year of discharge from the hospital. The late results of modified bed rest in their series showed that 3 per cent of the patients were dead and 4 per cent were chronically ill with tuberculosis. Badger and Ayvazian (17), presenting their experience in the follow-up of minimal disease in nurses, revealed essentially the same high rate of reactivation. Similar patients in a series at Fitzsimons Army Hospital, reported by Roper and Waring, revealed a reactivation rate after return to military duty of more than 50 per cent (18). Data thus far available at Fitzsimons Army Hospital, in patients treated with short-term chemotherapy, reveal a reactivation rate of approximately three to four times the reactivation rate in patients who received the same amount of chemotherapy but who also received resectional therapy (19).

Morphologically normal tubercle bacilli may be found on microscopy in

nearly all residual necrotic lesions and, if these bacilli could be proved dead by positive means, there would necessarily be a marked modification of the present-day surgical indications for the resection of such lesions. Improved culture methods, however, reveal an increasingly high percentage of cultures positive for tubercle bacilli, even from closed lesions. The physical and chemical environment in and around a necrotic residual lesion is most important in considering the status of these organisms. It seems likely, in the light of present evidence, that these bacilli are revivable with improved culture methods and hence offer potential hazards for future breakdown.

Careful pathologic study of all available residual necrotic lesions will gradually increase our knowledge of the behavior of such necrotic lesions and their response to chemotherapy. Thus, ultimately, it may be possible to classify these lesions with reasonable accuracy and to predict the treatment potentials and hazards of future relapse from these lesions in the individual patient.

The present problem is to decide whether long-term chemotherapy alone is sufficient or whether certain lesions are inherently hazardous pathologically and demand surgical resection plus long-term chemotherapy to minimize the possibility of relapse. No final statement is possible at this time, but the preliminary follow-up data indicate a favorable difference on the side of the patients who have been treated by surgery plus prolonged chemotherapy. Thus, at the present time certain of these residuals seem to present definite surgical indications; others may probably be safely treated by long-term chemotherapy; and certain others represent a group in which both resection and long-term chemotherapy should be tried with later evaluation of the end results.

If carefully considered judgment indicates that surgery is the treatment of choice in an individual patient, certain advantages accrue from the study of resected specimens. Such a study offers a logical guide to future treatment, particularly if there are ipsilateral or contralateral residuals remaining *in situ*. Surgery removes the main focus of necrotic irreversible parenchymal disease. Resection is selective and conserves function and permits early rehabilitation of the patient. The rate of the reversal of infectiousness to date in patients undergoing sublobar resection at Fitzsimons Army Hospital is more than 98 per cent.

SUMMARY

The minimal lesion in the pre-chemotherapy era was not an innocuous focus. The minimal lesion following short-term chemotherapy likewise carried an appreciable hazard of future relapse.

The viability of the morphologically normal tubercle bacilli found in nearly all residual lesions is unsettled. Present culture methods seem inadequate. The weight of evidence suggests that the bacilli may be revivable and hence potentially hazardous in terms of future relapse.

Pathologic study offers a means of evaluating the behavior and response to treatment of these necrotic residuals. Only in this way can the decision for or against resection be made with equal safety to the patient in future years. Surgical resection is mandatory in some necrotic residuals and contraindicated in others. A third group in which the surgical indication is not clear must remain

under study for later comparison with the results of long-term chemotherapy alone.

Surgical resection offers certain advantages, such as selective conservation of function, removal of the main necrotic irreversible focus, a high rate of reversal of infectiousness, and a logical guide to future treatment, particularly if residual lesions remain *in situ*. The surgical mortality is demonstrably low (less than 1 per cent). The immediate morbidity of resection must be balanced against the hazard of later relapse which, though serious, does not ordinarily threaten life.

The concepts of the management of the residual necrotic tuberculous lesion following long-term chemotherapy presented in the present review are based on a study of more than three hundred and fifty sublobar resections performed in Fitzsimons Army Hospital during the three and one-half year period, June, 1951, through December, 1954. Reversal of infectiousness in these patients to date is nearly 100 per cent.

SUMARIO

El Estado Actual de la Resección Pulmonar en el Tratamiento de los Residuos Esfacelados Localizados de la Tuberculosis Pulmonar: Repaso

La lesión mínima de la era prequimioterapéutica no era un foco inocuo. La consecutiva a la quimioterapia de poca duración llevaba igualmente un riesgo apreciable de futuras recidivas.

La viabilidad de los bacilos tuberculosos morfológicamente normales descubiertos en casi todas las lesiones residuales está irresuelta. Los actuales métodos de cultivo parecen inadecuados. La mayoría de los datos sugiere que los bacilos pueden ser revivibles y, por ello, potencialmente peligrosos en términos de futuras recidivas.

El estudio histopatológico ofrece un medio de justipreciar el comportamiento y la respuesta terapéutica de esos residuos esfacelados. Unicamente de ese modo podemos decidir en pro o en contra de la resección con seguridad igual para el enfermo en los años por venir. La resección quirúrgica es obligatoria en algunos residuos esfacelados y está contraindicada en otros. Un tercer grupo en el que la indicación quirúrgica no es clara debe permanecer bajo estudio para comparación más tarde con los resultados de la quimioterapia sola a largo plazo.

La resección quirúrgica ofrece ciertas ventajas, como son la conservación selectiva de la función, la extirpación del principal foco irreversible esfacelado, el viraje del esputo en alto grado y una orientación lógica del tratamiento futuro, en particular si los residuos permanecen *in situ*. La mortalidad quirúrgica es reconocidamente baja (menos de 1 por ciento). Hay que contrapesar la morbidad inmediata de la resección con el peligro de una recidiva subsiguiente, la cual, aunque grave, no amenaza ordinariamente la vida.

Los conceptos presentados en la comunicación actual acerca de la asistencia de la lesión tuberculosa esfacelada residual a continuación de la quimioterapia de largo plazo se basan en un estudio de más de 350 resecciones sublobulares ejecutados en el hospital Militar Fitzsimons durante el período de tres años y medio, junio, 1951–diciembre, 1954. En estos enfermos, el viraje de la infecciosidad hasta la fecha es casi de 100 por ciento.

RESUME

L'état actuel de l'exérèse pulmonaire dans le traitement des lésions résiduelles des foyers nécrosés de la tuberculose pulmonaire: Revue générale

La lésion minimale de l'ère pré-chimiothérapeutique n'était pas un foyer sans danger. De même, la lésion minimale succédant à une chimiothérapie à court terme comporte un risque appréciable de rechûtes ultérieures.

La viabilité des bacilles tuberculeux morphologiquement normaux découverts dans presque toutes les lésions résiduelle est indéterminée. Les méthodes de culture actuelles paraissent inadéquates. De nombreuses données suggèrent que les bacilles peuvent être ranimés et qu'ils sont potentiellement dangereux en ce qui concerne la rechûte éventuelle.

L'étude de la pathologie offre un moyen d'évaluer le comportement et la réponse au traitement de ces lésions nécrotiques résiduelles. Ce n'est que de cette manière que nous pourrons baser avec précision notre décision pour ou contre la résection, en assurant une même sécurité au patient dans les années à venir. L'exérèse est obligatoire dans certaines séquelles de lésions nécrotiques et contre-indiquée dans d'autres. Un troisième groupe, pour lequel l'indication chirurgicale n'est pas claire, doit rester à l'etude pour comparaison ultérieure avec les résultats procurés exclusivement par la chimiothérapie à long terme.

La chirurgie d'exérèse offre certains avantages, tels que la préservation d'une fonction particulière, l'excision du foyer nécrotique principal irréversible, une très grande proportion de négativation des crachats et constitue un guide logique quant au traitement ultérieur, en particulier lorsque des lésions résiduelles persistent *in situ*. La mortalité chirurgicale est démonstrativement basse (moins de 1%). La morbidité immédiate de la résection doit être évaluée par rapport au risque d'une rechûte ultérieure; ce risque tout en étant sérieux, ne menace pas ordinairement la vie.

Les conceptions du traitement des lésions tuberculeuses nécrosées résiduelles à la suite de la chimiothérapie à long terme, qui sont présentées dans ce rapport, sont fondées sur l'étude de plus de 350 résections sublobaires effectuées au Fitzsimons Army Hospital durant une période de 3 ans 1/2, de juin 1951, à décembre 1954. A ce jour, l'état d'infectiosité a été inversé, la proportion des cas abacillifères est presque de 100%.

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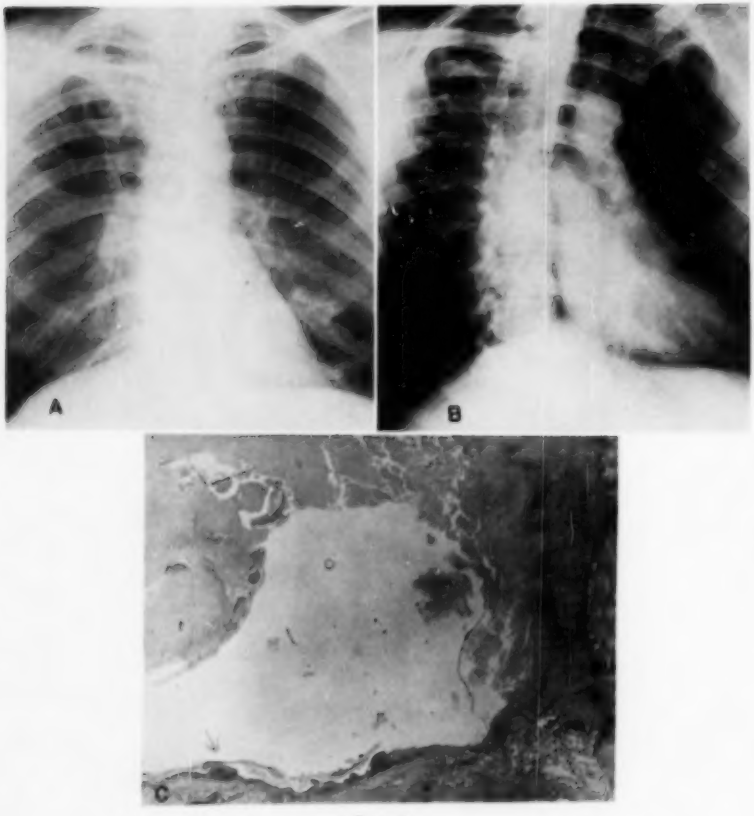
Figures for *Cases 1–13* follow



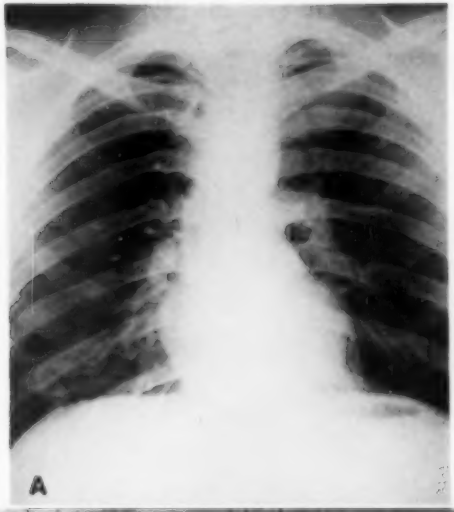
Case 1

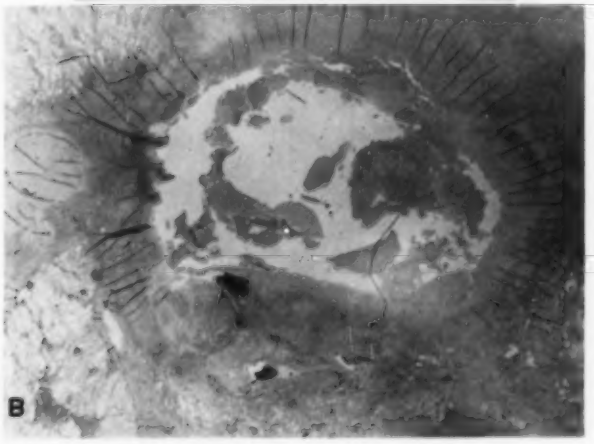
Open cavity: Male, 53 years of age. Symptoms of pulmonary tuberculosis began in October, 1951, with roentgenographic confirmation in June, 1952. Chemotherapy: isoniazid from October, 1952, to time of operation; streptomycin from January, 1953, to time of operation. Clinical improvement, August, 1953, except that the cavity increased in size. Sputum was infectious prior to surgery. Bronchoscopy was normal. Preliminary modified thoracoplasty, December, 1953. Right upper lobectomy in January, 1954.

A. October, 1953, roentgenogram showing right upper lobe cavity.

B. November, 1953, right anterior oblique view demonstrating right upper lobe cavity.

C. Gross section revealed a 2.7 cm. cavity in the posterior segment of the right upper lobe which was largely air-filled but also contained some soft caseous material. In an overall microscopic view, arrow indicates the site of mucosal squamous metaplasia at the bronchocavitary junction.





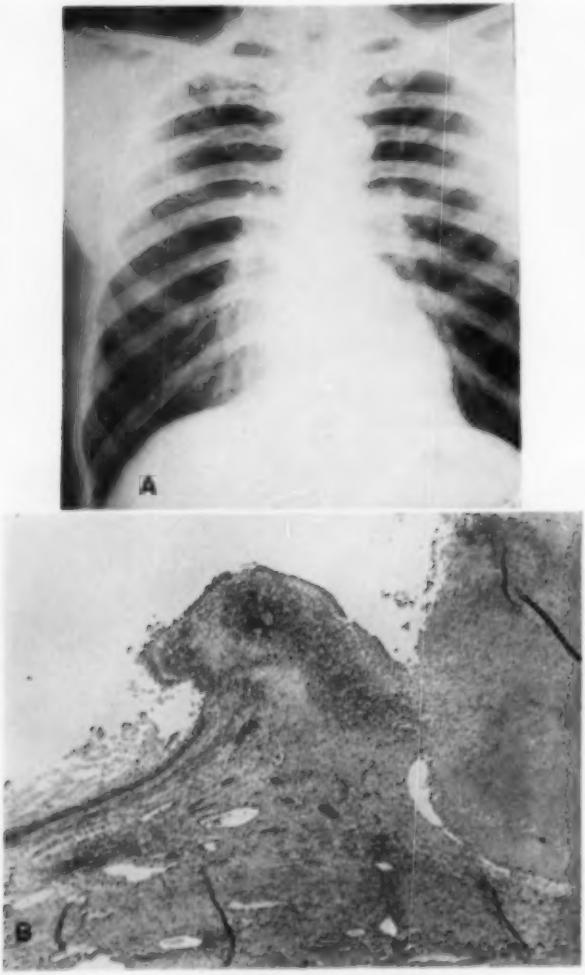
Case 2

Cavity by laminagram: Male, 20 years of age. Symptoms of pulmonary tuberculosis began in April, 1953, with roentgenographic confirmation in May, 1953. Sputum was infectious prior to surgery. Streptomycin and PAS therapy was begun in May, 1953. Bronchoscopy was normal. Basal segmental bronchiectasis on bronchograms. Basal segmental resection of the right lower lobe was performed in December, 1953, after seven months' combined intermittent therapy. Culture from operative specimen was positive for *M. tuberculosis*.

A. The original area of infiltration in the right lower lobe now suggests definite cavity which was confirmed on eccentric views and bronchograms. Grossly a cross section of the basal segments revealed a 2 by 1.5 by 1.2 cm. cavity in the posterior basal segment which was filled with creamy caseous material.

B. Under low power the microscopic view consisted of a pleural plaque, fibrous wall, and caseous lining.

An originally active cavitary ulcero-caseous lesion may be converted to a so-called inspissated cavity after prolonged chemotherapy. Closed or inspissated cavitary residuals are of various types pathologically as illustrated by *Cases 3* through *8*, inclusive.

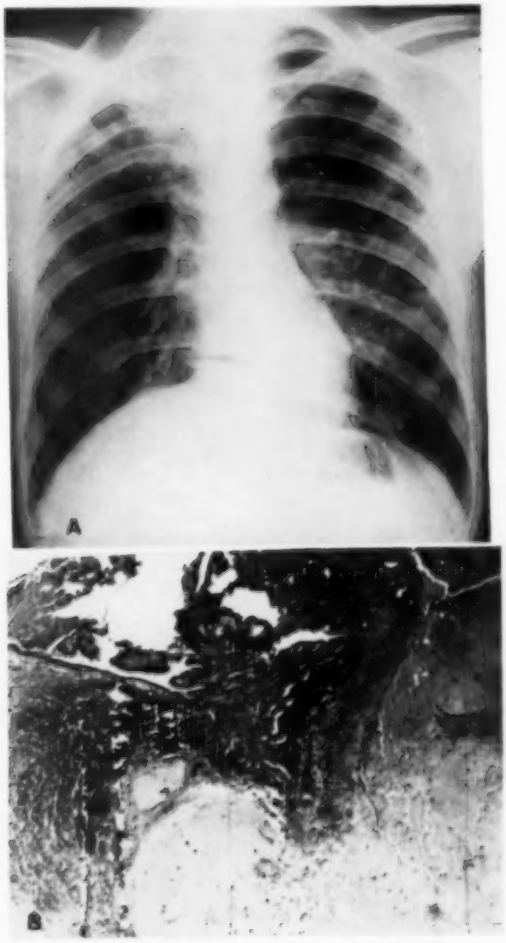


Case 3 (*See also Case 12*)

Patent bronchocavitary junction: Male, 47 years of age. Symptoms of pulmonary tuberculosis began in April, 1952, with roentgenographic confirmation in November, 1952. Sputum and culture were infectious on admission in May, 1953. Isoniazid-streptomycin therapy was begun in June, 1953. Apical posterior segment and a wedge of the anterior segment of the right upper lobe were removed in December, 1953.

A. Preoperative appearance of the chest in December, 1953. Gross specimen revealed a large pleural fibrous plaque 3 mm. in thickness overlying confluent lesions in the apical segment which on sectioning revealed ulcero-caseous and nodose disease.

B. Microscopic view: To the left the columnar respiratory epithelium can be seen. It ascends over a mass of scarred granulation tissue and exhibits squamous metaplasia as it dips down towards the inspissated caseous mass at the right.



Case 4

Bronchostenosis: Male, 30 years of age. Symptoms of pulmonary tuberculosis began in June, 1951, with roentgenographic confirmation at this time. Patient was admitted to the hospital in August, 1951. Isoniazid-streptomycin was given from July, 1952, to time of surgery. The patient's strain of tubercle bacilli was resistant to streptomycin in November, 1952, and to PAS in January, 1953. The last positive culture was obtained in October, 1952. A recurrent massive hemoptysis forced a right upper lobectomy in June, 1953.

A. Roentgenogram of chest during second admission in July, 1952.

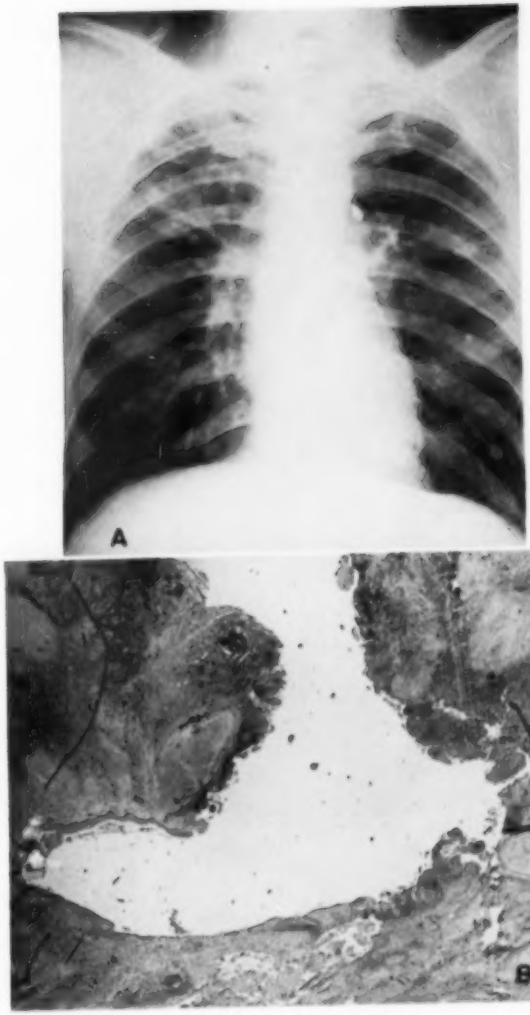
B. A high-powered view taken from the bronchiectatic segmental bronchus, with an area of bronchostenosis leading to a caseous focus. Dense fibrous connective tissue may be seen separating a 1.1 cm. inspissated lesion from the bronchial lumen at the upper left.

Case 5

Tangential bronchus: Female, 64 years of age. Admitted to Fitzsimons Army Hospital in December, 1953. Last normal roentgenogram was obtained in 1951. Symptoms of pulmonary tuberculosis began in December, 1953, and a roentgenogram obtained at this time revealed a "coin" lesion in the right upper lobe. Tumor could not be excluded and posterior segmental resection of the right upper lobe was performed in January, 1954. The operative specimen was positive for tubercle bacilli on microscopy and culture.

A. Roentgenogram reveals the lesion in the posterior segment as seen in the lordotic view on admission.

B. On gross sectioning there was a large circumscribed inspissated cavity in the posterior segment of the right upper lobe. The microscopic view reveals from left to right caseation, the fibrous wall of the lesion, and a tangential bronchus.

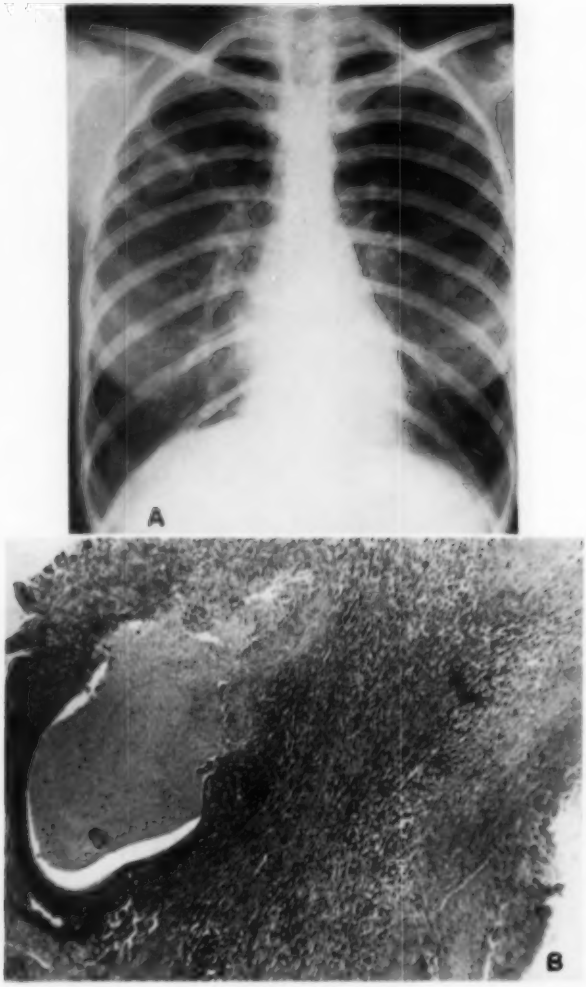


Case 6

Epithelized cystic cavity: Male, 42 years of age. Symptoms began and a diagnosis of pulmonary tuberculosis was made in December, 1951. Patient was admitted to Fitzsimons Army Hospital in September, 1952, after a massive hemoptysis. Sputum was positive for tubercle bacilli on microscopy and culture. Streptomycin-PAS therapy was given from March, 1951, to May, 1952. Isoniazid-streptomycin was administered for twenty months prior to surgery. Last culture positive for tubercle bacilli was obtained in March, 1954. Intermittent hemoptyses with right lower lobe spread occurred while patient was under therapy. Right upper lobectomy after modified thoracoplasty was performed in May, 1954, as a palliative procedure despite dangerous residual disease on the left.

A. Preoperative chest roentgenogram obtained in May, 1954.

B. A gross 2.5 cm. cavity in the posterior segment of the right upper lobe. This low-power microscopic view shows the dense fibrous wall of the cavity largely covered by stratified squamous epithelium seen best on the left and inferior aspects.



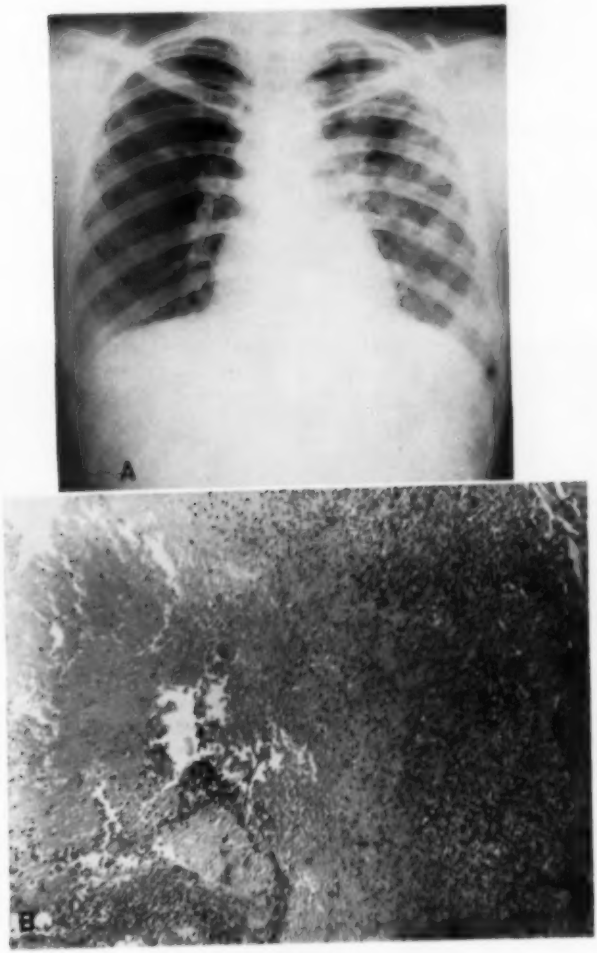
Case 7

Inspissated cavitary residuals may be associated with severe subsegmental endobronchial tuberculosis.

Female, 28 years of age, with symptoms of pulmonary tuberculosis, dating from January, 1953. Diagnosis was confirmed by roentgenogram and sputum culture in March, 1953. In May, 1953, isoniazid-streptomycin therapy was instituted. The cavity gradually inspissated. Posterior segmental resection of the right upper lobe was performed in November, 1953.

A. Roentgenogram of the chest one month prior to hospital admission.

B. Grossly there is a 2 cm. caseous lesion in the posterior segment of the right upper lobe, the posterior segmental bronchus being occluded by scar tissue. Microscopically caseous material containing demonstrable acid-fast bacilli has escaped into the lumen of the small bronchus. Active endobronchial tuberculosis with metaplasia at the bronchocavitary junction is seen.

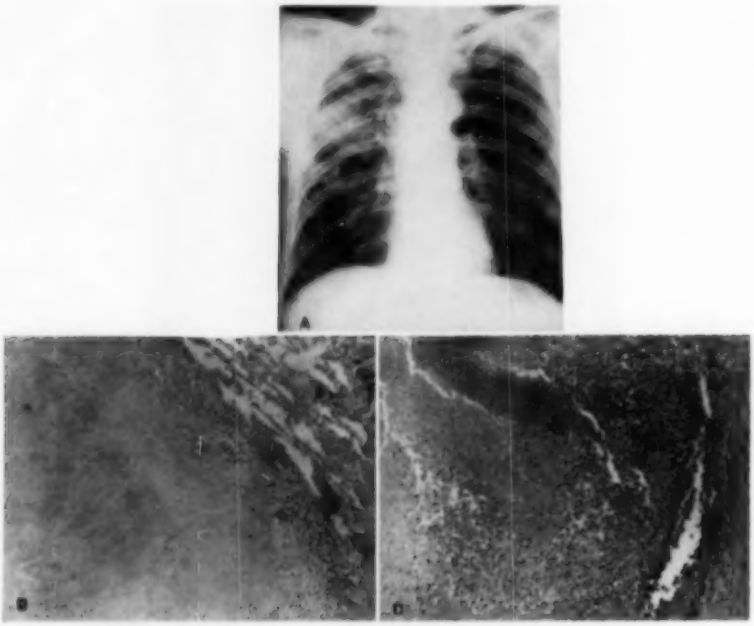


Case 8

Inspissated cavity with relapse: Female, 22 years of age. Symptoms of pulmonary tuberculosis confirmed by sputum culture in May, 1952. Hospitalized at this time and, until March, 1953, received isoniazid-streptomycin. Recurrent hemoptyses with infectious sputum in June, 1953. Isoniazid-streptomycin reinstituted at this time. Admitted to Fitzsimons Army Hospital in August, 1953. Sputum cultures positive for tubercle bacilli which were susceptible to streptomycin, PAS, and isoniazid. Recurrent episodes of hemoptysis in November, 1953. Bronchoscopy, normal. Operation in January, 1954, consisted of apical posterior segmental resection of the left upper lobe and a superior segmental resection of the left lower lobe. Cultures of the operative specimen were positive for tubercle bacilli.

A. Appearance of the chest in June, 1953, two days before hemoptysis.

B. Microscopic view of one of many similar foci showing severe chronic inflammation, caseation, and areas of liquefaction infiltrated by polymorphonuclear leukocytes.



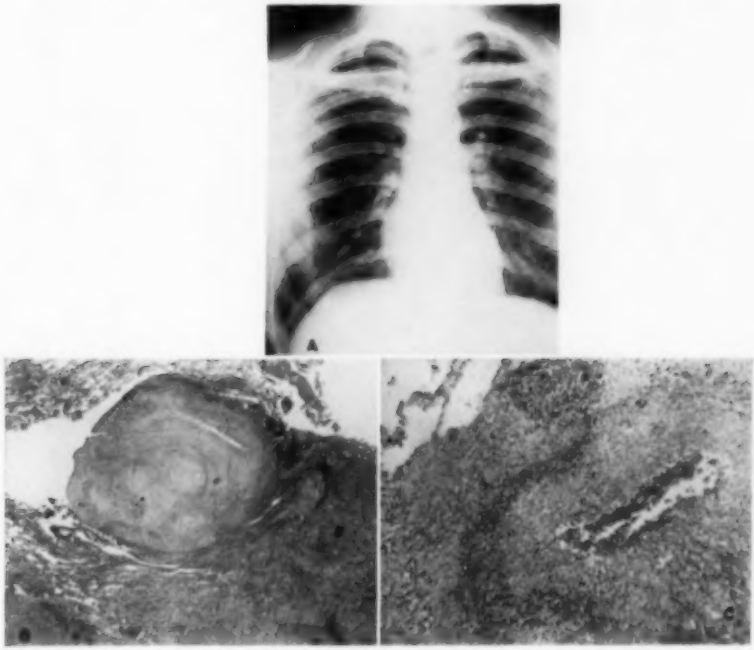
Case 9

Old, chronic relapsing disease: Male, 56 years of age; known diabetic for seven years. Sputum positive for tubercle bacilli in January, 1953. Patient was admitted to Fitzsimons Army Hospital in February, 1953. Bronchial washings were positive for tubercle bacilli on culture in March, 1953. Isoniazid-streptomycin and PAS were given for fourteen months before operation in April, 1954, consisting of right upper lobectomy and wedge resection of superior segment of the right lower lobe.

A. Roentgenogram of the chest on admission in February, 1953.

B. Microscopic view reveals the well-advanced organization of the caseous center. The capsular region shows no active tuberculous disease although mild chronic inflammation persists.

C. This separate lesion shows remnants of a dense fibrous capsule to the right while centrally there is fresh caseation necrosis with chronic and acute inflammation.



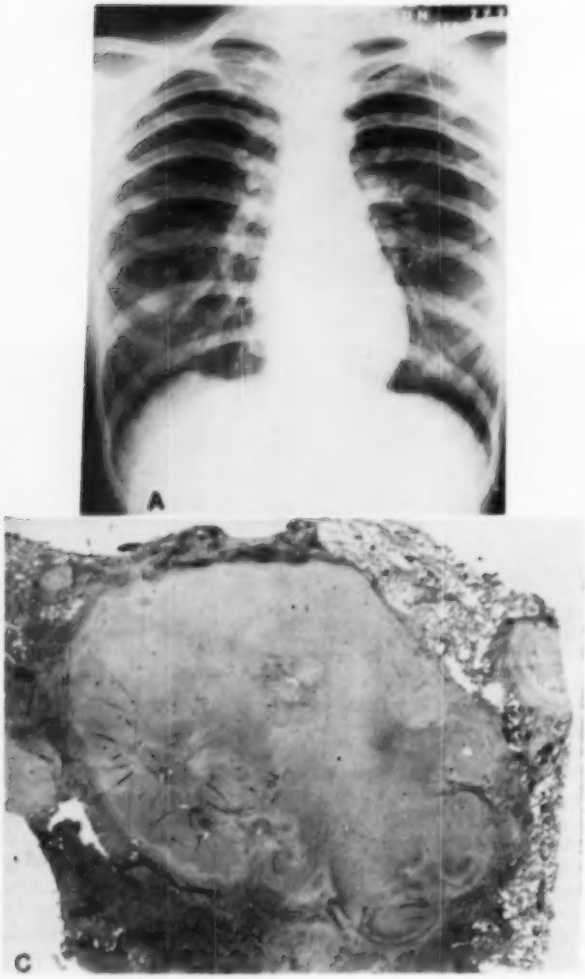
Case 10

Clinical or bacteriologic activity: Male, 28 years of age; tuberculous lesion first noted on separation examination. He was admitted to Fitzsimons Army Hospital in August, 1953. Chest roentgenogram in 1948 was normal. Precursor to the present lesion was noted in 1949 but was regarded as stable. Bacteriologic findings were negative. Isoniazid-streptomycin was begun in August, 1953, and apical posterior segmental resection of the left upper lobe was carried out in January, 1954. Microscopy and guinea pig inoculations of the specimen were positive for tubercle bacilli.

A. Admission chest roentgenogram obtained in August, 1953.

B. This lesion is well hyalinized and appears quite inactive. The surrounding pulmonary tissue however exhibits chronic organizing pneumonia.

C. In this microscopic view, active tuberculous disease is present in this lesion as shown by the epithelioid cell proliferation, multiplicity of Langhans' giant cells, and early caseous necrosis associated with infiltration of many polymorphonuclear leukocytes.

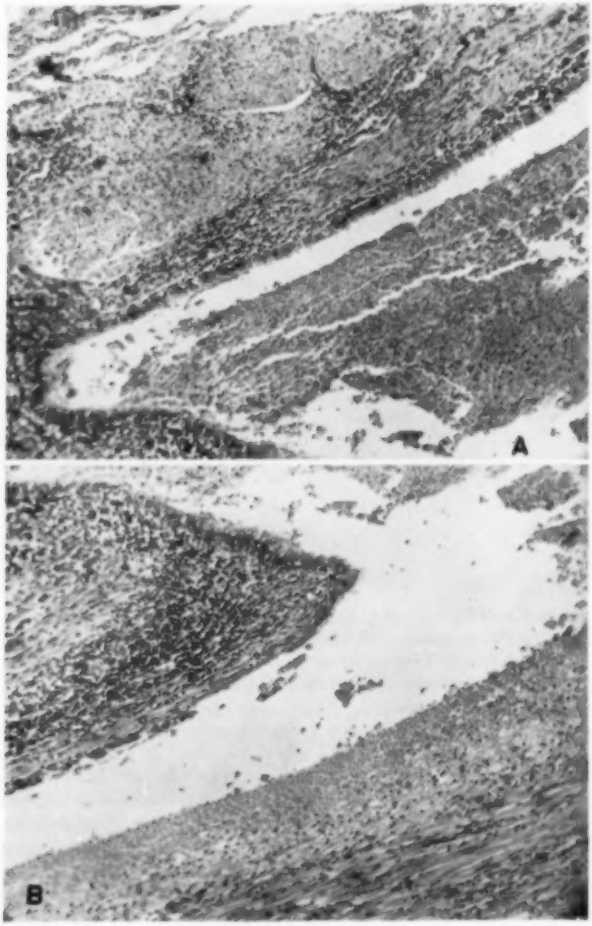


Case 11

Solid residual lesion, more than 1.5 cm. Female, 27 years of age, admitted in September, 1953. Last normal roentgenogram was obtained in January, 1952. Symptoms and roentgenographic findings of tuberculosis in June, 1952. Tuberculin reaction was positive; the sputum was noninfectious. Isoniazid-streptomycin was given for eight weeks, followed by wedge resection of the lesion in the superior segment of the right lower lobe. Microscopy specimen was positive for acid-fast bacilli.

A. Roentgenogram of the chest in June, 1952.

C. Microscopic view showing in the upper left incorporation of "daughter" granulomas in progress. Chronic organizing pneumonia involving the adjacent pulmonary tissue. One small bronchus contains caseous material.

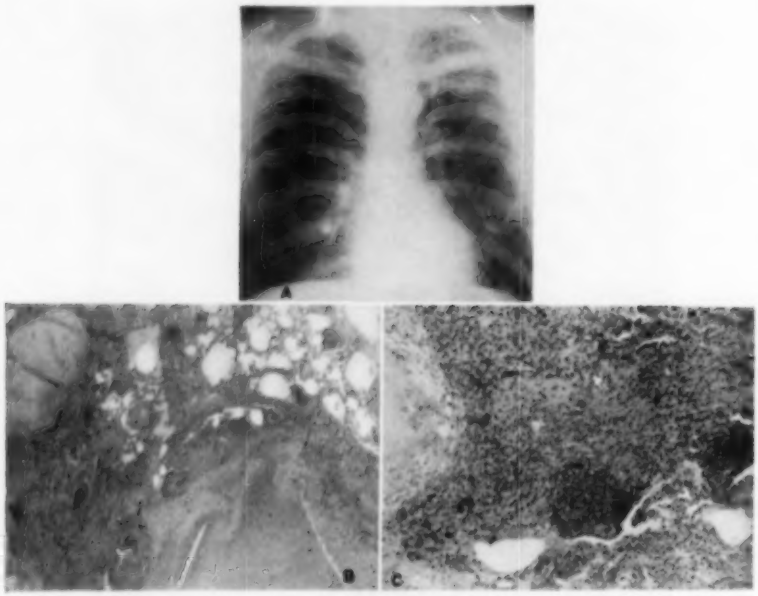


Case 12 (See also Case 3)

Active tuberculous bronchial disease: Male, 47 years of age. Symptoms of pulmonary tuberculosis began in April, 1952. First abnormal roentgenogram was obtained in November, 1952. Sputum was infectious on hospital admission in May, 1953. Isoniazid-streptomycin was begun in June, 1953. Apical posterior segment and a wedge of the anterior segment of the right upper lobe was removed in December, 1953.

A. Dilated peripheral bronchiole away from the hilus. Top left reveals caseous matter in the alveoli. The lumen of the bronchus contains very necrotic material with tubercle bacilli.

B. The top wall of the bronchiole reveals degenerative squamous cells with ulceration. Lower wall shows caseation, foam cells, loss of mucous membrane lining, and peripheral fibrosis in the bronchial wall.



Case 13

Localized tuberculous residuals remaining after prolonged chemotherapy and ordinarily suitable for observation may become surgical indications if situated in damaged, poorly ventilated, inadequately draining areas of lung due to a chronic organizing pneumonitis or localized bronchiectasis.

Male, 39 years of age. First abnormal roentgenogram was obtained in August, 1952. Symptoms began in September, 1952. Patient was admitted to Fitzsimons Army Hospital in November, 1952. Sputum contained tubercle bacilli on microscopy and culture. Emphysema noted by clinical roentgenography and pulmonary function studies. Streptomycin—PAS started on admission. Apical posterior segmental resection of the left upper lobe was carried out in August, 1953.

A. Admission chest roentgenogram in October, 1952.

B. To the right there is a large focus showing softening of its caseous contents. At the upper left there is an inactive, hyalinized caseonodose lesion. Note the fibrous scarring of the intervening parenchyma.

C. There is irreversible destruction of the pulmonary tissue associated with much chronic inflammation.

LARGE-SCALE JURY TYPE OF REVIEW OF THE INDICATIONS FOR SURGERY IN PULMONARY TUBERCULOSIS[1,2]

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INTRODUCTION

Changes in the therapy of pulmonary tuberculosis since 1946 have taken place so rapidly as to assume a kaleidoscopic character. Methods of treatment which seemed firmly established by usage and tradition have been uprooted. The area of application of other methods has become so limited that they are on the verge of obsolescence.

In the field of surgery within the past decade internal pneumonolysis, phrenic nerve operations, extrapleural pneumothorax, and plombage have been virtually abandoned. Cavernostomy has become a strictly salvage procedure, and even time-honored multiple-stage thoracoplasty is fighting for survival. The present writers have been concerned lest there be too rapid an abandonment of all the old procedures. They have also wondered whether the enthusiasm for resection was as widespread as its supporters contend. In short, is the trend toward "a resection or nothing" position winning the field by default? Accordingly, the present investigation was undertaken in order to determine the actual present-day trend of the surgical management of pulmonary tuberculosis in the United States.

MATERIAL AND METHODS

A series of 12 patients was selected whose pulmonary lesions presented a cross section of the various types of problem presented to the usual surgical therapy boards. Representative films covering the entire period of the tuberculosis history of these patients were selected and reduced to 8- by 10-inch size. A folder was made of these films which also included an abstract of the clinical history. These twelve folders were mailed to fifty thoracic surgeons and fifty-three thoracic internists who were closely identified with the therapy of pulmonary tuberculosis. An attempt was made to obtain representation from all of the geographic areas of the United States. The participants were asked to indicate the type of therapy they would select for each patient after a study of the history and series of films. It was requested that the philosophy of treatment currently in use be adopted as the basis for selection.[3] The recommendations of these 103 physicians have been tabulated and are presented. When more than one recommendation was made, the first mentioned was considered the choice and was used for tabulation.

[1] From the Veterans Administration Hospital, Oteen, North Carolina.

[2] Presented before the Medical Session, as part of *Section 3A*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 24, 1955.

[3] Trimble and Eton made a similar study, from a medical viewpoint, in 1955 (Dis. of Chest, 1955, *27*, 1).

TABLE 1

SUGGESTED TREATMENT OF A PATIENT WITH AN INSPISSATED CAVITY 1.5 CM. IN DIAMETER AND SPUTUM NEGATIVE FOR M. TUBERCULOSIS

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Wedge or subsegmental resection	2	4	1	2.0	3	2.9
Segmental resection	23	46	23	44.2	46	45.1
Without further therapy	(22)		(23)			
With concomitant thoracoplasty	(1)		(0)			
Resection, type not stated	0		2	3.8	2	2.0
"Randomize" for resection	1	2	0		1	1.0
Thoracoplasty, Alexander type	1	2	0		1	1.0
No surgery	23	46	26	50.0	49	48.0
Total	50	100	52	100.0	102	100.0

CASE REPORTS

Case 1. R. T. S., a 46-year-old white male, had a left apical cavitary lesion which retrogressed to an inspissated cavity during treatment with streptomycin and para-aminosalicylic acid (PAS). As in all succeeding cases, the abstracted history presented in figure 1 is the same as was made available to the participants in the study. The chest roentgenogram, dated December 24, 1951 (figure 1*A*), shows the disease present at the onset of pulmonary tuberculosis. For comparison, a planigram of the left apex taken on January 26, 1953 (figure 2*B*) reveals the inspissated 1.5 cm. cavity overlying the third rib, posteriorly. Sputum was negative for tubercle bacilli for six months prior to consideration for surgery. The patient's original strain of tubercle bacilli was susceptible to streptomycin and PAS.

Recommendations by consultants: The recommendations for treatment are tabulated in table 1. It is interesting to note that the opinion of both surgeons and internists is almost equally divided in regard to surgical and nonsurgical treatment. The ideal treatment of this type of case can only be decided by randomization of a large series, as was suggested by one surgeon. Segmental resection was the most frequently suggested type of pulmonary resection, being considered by 46 per cent of the surgeons and 44.2 per cent of the internists. Thoracoplasty was considered by only one surgeon as definitive treatment. A second surgeon stated that he would do a concomitant thoracoplasty at the time of segmental resection.

Operative findings: At the time of operation the residual disease was sufficiently localized so that it could be removed by subsegmental resection. The thin-walled cavity was filled with pus and was surrounded by several small caseous nodules. Acid-fast bacilli were demonstrated on microscopy. The postoperative course was uneventful.

Case 2. W. C., a 28-year-old Negro male, had an inspissated 3 cm. cavity. The roentgenogram dated August 31, 1951 (figure 2*A*), showing maximal involvement by disease, was taken shortly after onset of pulmonary tuberculosis. For comparison, a film dated July 14, 1952 (figure 2*B*) shows the improvement prior to consideration for surgery. The sputum has remained negative for tubercle bacilli since the first few weeks of a ten-month course of treatment with streptomycin, PAS, and pneumoperitoneum.

TABLE 2

SUGGESTED TREATMENT OF A PATIENT WITH AN INSPISSATED CAVITY 3 CM. IN DIAMETER AND SPUTUM NEGATIVE FOR M. TUBERCULOSIS

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Wedge or subsegmental resection	3	6	0		3	2.9
Segmental resection	33	66	23	43.4	56	54.4
Lobectomy	4	8	6	11.3	10	9.7
Resection, type not stated	2	4	5	9.4	7	6.8
"Randomize" this type of case	2	4	0		2	1.9
No surgery	6	12	19	35.9	25	24.3
Total	50	100	53	100.0	103	100.0

Recommendations by consultants: The treatment recommended is presented in table 2. It will be noted that pulmonary resection was recommended by 84 per cent of the surgeons and 64 per cent of the internists. Segmental resection was considered more frequently than was lobectomy of portions of lung smaller than a segment. Two surgeons recommended that this type of case be "randomized" so that 50 per cent of such cases would be treated by pulmonary resection and 50 per cent treated medically in order to determine the best treatment. It appears that the surgeons are more eager to operate in this type of case than the internists, since only 6 of 50 surgeons (12 per cent) as compared to 19 of 53 internists (35.9 per cent) did not advise surgery. Thoracoplasty or additional drug treatment before resection was not recommended in this case.

Operative findings: This lesion was so well localized that resection of the posterior subsegment of the left upper lobe was sufficient to remove the disease. The inspissated cavity had a rather dense fibrous wall. Acid-fast organisms were demonstrated on microscopy. The postoperative course was uneventful.

Case 3. W. O. D., a 31-year-old white male, had bilateral upper lobe disease at onset with a nodule on the right and a thick-walled cavity on the left. The cavity in the left apex became inspissated during treatment with bed rest, but shortly after initiating pneumoperitoneum the cavity reopened. This history is presented in figure 3. The chest roentgenogram, obtained on October 17, 1950 (figure 3*A*), shows the type of disease found eight months after the diagnosis of pulmonary tuberculosis was made. For comparison a full chest planigram, taken on May 1, 1951 (figure 3*B*), shows the residual small nodule in the right upper lobe and a larger nodule in the left upper lobe revealing a small crescent area of cavitation. The patient had received streptomycin-PAS only three weeks before consideration for therapy.

Recommendations by consultants: The recommendations for treatment are tabulated in table 3. It will be noted that pulmonary resection of some type was recommended by 94 per cent of the surgeons and 90.6 per cent of the internists. Segmental resection was the most frequent recommendation, as was suggested by 74 per cent of the surgeons and 58.5 per cent of the internists. Wedge or subsegmental resection was recommended by the combined group as often as was lobectomy. Further drug therapy before resection was recommended by

TABLE 3

SUGGESTED TREATMENT OF A PATIENT WITH RECURRENCE OF A PREVIOUSLY INSPISSATED CAVITY AND SPUTUM POSITIVE FOR TUBERCLE BACILLI

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Wedge or subsegmental resection	4	8	4	7.5	8	7.8
Segmental resection	37	74	31	58.5	68	66.0
Without further therapy	(34)		(25)			
After further drug therapy	(3)		(6)			
Lobectomy	2	4	6	11.4	8	7.8
Without further therapy	(1)		(3)			
After further drug therapy	(1)		(3)			
Resection, type not stated	4	8	7	13.2	11	10.6
Without further therapy	(2)		(5)			
After further drug therapy	(2)		(2)			
No surgery	3	6	5	9.4	8	7.8
Total	50	100	53	100.0	103	100.0

12 per cent of the surgeons and 20.8 per cent of the internists. Thoracoplasty was not recommended either as definitive treatment or in conjunction with pulmonary resection. Even though there was roentgenographic evidence of cavitation and sputum was positive for *M. tuberculosis*, 7.8 per cent of the entire group recommended only medical treatment.

Operative findings: Since the lesion was well localized, the disease was removed by subsegmental resection. The 2.5 cm. cavity was well encapsulated by fibrous tissue and a communicating bronchus revealed ulcerative tuberculosis. Caseous material from the cavity produced tuberculosis in the inoculated guinea pig. The postoperative course was uneventful.

Case 4. C. E. P. At onset this 19-year-old white male had bilateral disease which cleared on treatment with isoniazid-streptomycin to a thin-walled, so-called "isoniazid" cavity. A chest roentgenogram, dated September 18, 1953 (figure 4*A*), shows the status of the pulmonary tuberculosis two months after the onset of illness. The second roentgenogram, dated July 15, 1954 (figure 4*B*), shows the residual left apical cavity. As noted in the history the sputum was negative for acid-fast bacilli for five months before consideration for surgery. There was bacterial resistance to streptomycin concentrations of 10 γ per ml.

Recommendations by consultants: According to the recommendations listed in table 4, it may be seen that the majority of both groups, that is, 86 per cent of the surgeons and 90.4 per cent of the internists, agreed on pulmonary resection for this so-called "isoniazid" cavity. This is interesting in view of the fact that the sputum had been negative for tubercle bacilli for a five-month period before a decision on the question of surgery. Segmental resection was recommended more frequently. This procedure was preferred by 46 per cent of the surgeons and 50 per cent of the internists. Lobectomy was considered the choice by 18 of 50 surgeons (36 per cent) and by 15 of 52 internists (28.9 per cent). Thoracoplasty was advised as the definitive treatment by 6 per cent of the surgeons and

TABLE 4

SUGGESTED TREATMENT OF THE SO-CALLED "ISONIAZID" CAVITY

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Wedge or subsegmental resection	0		1	1.9	1	1.0
Segmental resection	23	46	26	50.0	49	48.0
Without further therapy	(21)		(24)			
After further drug therapy	(1)		(0)			
With concomitant thoracoplasty	(1)		(0)			
With prior thoracoplasty	(0)		(1)			
With postoperative pneumoperitoneum	(0)		(1)			
Lobectomy	18	36	15	28.9	33	32.3
Without further therapy	(10)		(12)			
After further drug therapy	(0)		(1)			
With prior Alexander thoracoplasty	(1)		(0)			
With prior plombage thoracoplasty	(1)		(0)			
With concomitant thoracoplasty	(6)		(1)			
With subsequent thoracoplasty	(0)		(1)			
Resection, type not stated	2	4	5	9.6	7	6.9
Without further therapy	(1)		(4)			
After further drug therapy	(0)		(1)			
With concomitant thoracoplasty	(1)		(0)			
Thoracoplasty	3	6	4	7.7	7	6.9
Alexander	(1)		(3)			
Plombage	(2)		(1)			
No surgery	4	8	1	1.9	5	4.9
Total	50	100	52	100.0	102	100.0

by 7.7 per cent of the internists. As an adjunct to pulmonary resection, thoracoplasty was considered by 10 of 50 surgeons and by 3 of 52 internists. Postoperative pneumoperitoneum following segmental resection was suggested by one internist. Only one surgeon and 2 internists thought that the patient should have further drug therapy before resection. Four surgeons (8 per cent) and one internist (1.9 per cent) did not recommend surgery.

Operative findings: This patient was treated by a two-stage six-rib thoracoplasty. The sputum became positive for tubercle bacilli following thoracoplasty, so an apical-posterior segmental resection was performed three months after the first-stage thoracoplasty. A small nodule in the lingula was also removed by wedge resection. The wall of the 5 cm. cavity consisted of rather uniform hyalinized fibrous tissue containing giant cells and macrophages in a few areas. Acid-fast bacilli were demonstrated on microscopy. Secondary bronchiectasis was present in the resected specimen. The postoperative course was uneventful following resection.

Case 5. W. G. S., a 33-year-old white male, had an open cavity in the right upper lobe associated with sputum positive for tubercle bacilli which showed some resistance to various antituberculous drugs. The patient had bilateral apical cavitary pulmonary tuberculosis,

as is noted in the chest roentgenogram dated May 5, 1947 (figure 5*A*), obtained four months after onset of his disease. He was treated with left phrenic nerve crush and pneumoperitoneum. He developed a spread of tuberculosis in the right upper lung a short time after a ten-month course of streptomycin-PAS was discontinued. It was then noted that he had developed bacterial resistance to streptomycin concentrations of 10 γ per ml. He was started on a second course of isoniazid-streptomycin six months before consideration for surgery. The cavity in the left apex was considered closed and the spread in the right upper lobe had disappeared, as will be noted on the second roentgenogram, dated January 29, 1954 (figure 5*B*).

Recommendations by consultants: The recommendations for treatment are set forth in table 5. There was complete agreement by both surgeons and internists on the need for surgical treatment. Segmental resection was recommended by 54 per cent of the surgeons and by 39.6 per cent of the internists. Lobectomy was preferred by 26 per cent of the surgeons and by 32.1 per cent of the internists. Bilateral resection was considered the treatment of choice by 3 of 50 surgeons and by 5 of 53 internists. One surgeon and one internist thought that this patient needed further drug treatment before surgery. Thoracoplasty was recommended by only 2 of 50 surgeons and 5 of 53 internists. A concomitant thoracoplasty at the time of pulmonary resection was recommended by 4 surgeons and one

TABLE 5

SUGGESTED TREATMENT OF A PATIENT WITH AN OPEN CAVITY AND SPUTUM POSITIVE FOR TUBERCLE BACILLI PARTIALLY DRUG-RESISTANT

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Wedge or subsegmental resection	0		1	1.9	1	1.0
Segmental resection	27	54	21	39.6	48	46.6
Without further therapy	(25)		(21)			
With concomitant thoracoplasty	(1)		(0)			
After further drug therapy	(1)		(0)			
Lobectomy	13	26	17	32.1	30	29.2
Without further therapy	(9)		(15)			
After further drug therapy	(0)		(1)			
With concomitant thoracoplasty	(2)		(1)			
With subsequent thoracoplasty	(1)		(0)			
Also pneumoperitoneum	(1)		(0)			
Bilateral resection	3	6	5	9.4	8	7.7
Without further treatment	(3)		(4)			
After further drug therapy	(0)		(1)			
Resection, type not stated	5	10	4	7.5	9	8.7
Without further therapy	(4)		(4)			
With prior plombage thoracoplasty	(1)		(0)			
Thoracoplasty	2	4	5	9.5	7	6.8
Alexander	(0)		(3)			
Paulino	(1)		(0)			
Plombage	(1)		(2)			
Total	50	100	53	100.0	103	100.0

internist. One surgeon stated he would recommend a plombage thoracoplasty prior to resection, while 2 surgeons would have performed post-resection thoracoplasty, one of whom stated he would also add pneumoperitoneum.

Operative findings: A three-rib right posterolateral thoracoplasty was followed in six weeks by a right upper lobectomy. In addition to a 3 cm. cavity in the posterior segment, nodular disease was found in all segments of the right upper lobe. Proliferative tubercles without necrosis were found near the cavity and tubercle bacilli were demonstrated by microscopy. Tuberculous ulceration was present in a small bronchus. The postoperative course was uneventful.

Case 6. E. T. K., a 29-year-old white male, had an open tuberculous cavity associated with sputum negative for tubercle bacilli for more than three months. The chest roentgenogram, dated October 12, 1952 (figure 6*A*), was obtained four months after onset of the tuberculosis. A spread of the disease to the left midlung field from a cavitary lesion in the right apex was seen. The patient was treated with pneumoperitoneum and various courses of antituberculous drugs, as will be noted in the abstracted history (figure 6). The chest roentgenogram, dated February 26, 1954 (figure 6*B*), shows the amount of improvement present before consideration for surgery. Planigrams substantiated the presence of a cavity in the upper lobe. Bacterial resistance to streptomycin, PAS, isoniazid, and viomycin was present.

Recommendations for treatment: In table 6, it may be noted that the entire group of consultants recommended surgical treatment except 4 of the 53 internists. Pulmonary resection was recommended by 34 of 50 surgeons (68 per cent) and 31 of 53 internists (58.5 per cent). Lobectomy was suggested more frequently than other types of resection, being considered by 39.8 per cent of the entire group. Lobectomy plus a wedge or segmental resection was preferred by 7 surgeons (14 per cent) and by one internist. Bilateral resection was recommended by 2 internists. Thoracoplasty was the primary procedure of choice among 32 per cent of the surgeons and 34 per cent of the internists, the Alexander type being the most popular. Thoracoplasty as an adjunct to pulmonary resection was advised by 30 per cent of the surgeons and by 11.3 per cent of the internists. Concomitant thoracoplasty was most frequently recommended by both groups, being considered twice as often as both prior and subsequent thoracoplasty. Two internists stated that they would give drug therapy for an additional period before proceeding with surgical treatment.

Operative findings: An Alexander two-stage, six-rib thoracoplasty was followed by sputum continuously positive for tubercle bacilli. Five months after thoracoplasty, a right upper lobectomy was carried out without further antituberculous chemotherapy. Caseous nodular disease was generally confined to the apical and posterior segments. A bronchus was found to communicate with the center of one caseous nodule. Secondary bronchiectasis was seen on sections of the small bronchi. Acid-fast organisms were not demonstrated in the tissues. The postoperative course has remained uneventful except for a *Staphylococcus aureus* wound infection which responded well to incision and drainage.

Case 7. O. E. B., a 37-year-old Negro male, had cavitary tuberculosis of the lung with bacilli resistant to antituberculous drugs 2.5 months before consideration of surgical

TABLE 6

SUGGESTED TREATMENT OF A PATIENT WITH AN OPEN CAVITY AND SPUTUM NEGATIVE FOR TUBERCLE BACILLI AND DRUG-RESISTANT

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Wedge or subsegmental resection	2	4	2	3.8	4	3.9
After further drug therapy	(0)		(1)			
With prior thoracoplasty	(1)		(1)			
With concomitant thoracoplasty	(1)		(0)			
Segmental resection	0		4	7.5	4	3.9
Lobectomy	21	42	20	37.7	41	39.8
Without further therapy	(14)		(14)			
With prior thoracoplasty	(0)		(1)			
With prior and concomitant thoracoplasty	(1)		(0)			
With concomitant thoracoplasty	(4)		(4)			
With subsequent thoracoplasty	(1)		(0)			
With postoperative pneumoperitoneum	(1)		(1)			
Lobectomy plus wedge or segment	7	14	1	1.9	8	7.8
Without further therapy	(2)		(1)			
With concomitant thoracoplasty	(4)		(0)			
With subsequent thoracoplasty	(1)		(0)			
Resection, type not stated	4	8	2	3.8	6	5.8
Without further therapy	(2)		(2)			
With prior plombage thoracoplasty	(1)		(0)			
With concomitant thoracoplasty	(1)		(0)			
Bilateral resection	0		2	3.8	2	1.9
Thoracoplasty	16	32	18	34.0	34	33.0
Plombage type	(5)		(7)			
Alexander type	(11)		(10)			
After further drug treatment	(0)		(1)			
No surgery	0		4	7.5	4	3.9
Total	50	100	53	100.0	103	100.0

therapy. At first, the disease was confined to the right upper lobe, but eventually the patient developed a spread to the right lower- and left midlung fields, as will be noted on the roentgenogram, dated February 25, 1952 (figure 7*A*). Comparison with the second chest film, dated September 22, 1953 (figure 7*B*), will show clearing of this more recent process.

Recommendations by consultants: There was general agreement in the two groups of consultants with respect to resectional therapy in this case. Resection was recommended by 84 per cent of the surgeons and 83.1 per cent of the internists. Lobectomy was the most commonly recommended treatment and was recommended by 72 per cent of the surgeons and 77.4 per cent of the internists. Resection of less than a lobe (segmental) was considered by only one surgeon. Eight surgeons (16 per cent) and 8 internists (15 per cent) recommended thoracoplasty as the primary treatment of choice. Thoracoplasty as an adjunct to resection was advised by 15 surgeons (30 per cent) and 13 internists (24.5 per cent). As will be noted in table 7, only one internist in the combined group

TABLE 7

SUGGESTED TREATMENT OF A PATIENT WITH AN OPEN CAVITY AND SPUTUM POSITIVE FOR TUBERCLE BACILLI AND DRUG-RESISTANT

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Segmental resection	1	2	0		1	1.0
Lobectomy	36	72	41	77.4	77	74.6
Without further therapy	(23)		(27)			
After further drug therapy	(1)		(1)			
Prior Alexander thoracoplasty	(2)		(1)			
Prior plombage thoracoplasty	(1)		(1)			
With concomitant thoracoplasty	(8)		(6)			
After further drug therapy and pneumoperitoneum	(0)		(1)			
Subsequent thoracoplasty	(1)		(2)			
Subsequent thoracoplasty and pneumoperitoneum	(0)		(1)			
Subsequent pneumoperitoneum	(0)		(1)			
Lobectomy plus wedge or segment	2	4	0		2	2.0
Prior thoracoplasty	(1)					
Concomitant thoracoplasty	(1)					
Resection, type not stated	3	6	3	5.7	6	5.9
Without further therapy	(2)		(2)			
After further drug therapy	(0)		(1)			
With prior plombage thoracoplasty	(1)		(0)			
Thoracoplasty	8	16	8	15.0	16	15.5
Alexander type	(8)		(7)			
Plombage type after further drug therapy	(0)		(1)			
No surgery	0		1	1.9	1	1.0
Total	50	100	53	100.0	103	100.0

recommended no surgery. Further drug therapy was recommended by one surgeon before lobectomy, while 2 internists (3.8 per cent) preferred further drug therapy before resection, and one (1.9 per cent) before thoracoplasty. Another internist (1.9 per cent) recommended drug therapy and pneumoperitoneum followed by lobectomy and concomitant thoracoplasty.

Operative findings: A two-stage thoracoplasty, with the removal of ribs one through seven, was performed in this patient. A spread of tuberculosis to the left lower lobe followed the second-stage thoracoplasty. Approximately three months after the second-stage thoracoplasty and five weeks after changing drug therapy to isoniazid and pyrazinamide, a right upper lobectomy was done for sputum persistently positive for tubercle bacilli and residual cavitation. Acid-fast organisms were present in the surgical specimen. Nodular disease (less than 1 cm. in diameter) was left in the remaining lung; the patient had an uneventful postoperative course.

Case 8. O. J., a 29-year-old Negro male, had bronchiectasis associated with pulmonary tuberculosis. The abstracted history is presented in figure 8. The roentgenogram of January

TABLE 8

SUGGESTED TREATMENT OF BRONCHIECTASIS ASSOCIATED WITH PULMONARY TUBERCULOSIS

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Lobectomy	22	44	29	54.7	21	49.5
Without further therapy	(12)		(19)			
With concomitant thoracoplasty	(1)		(0)			
With subsequent thoracoplasty	(0)		(2)			
With prior thoracoplasty	(9)		(8)			
Lobectomy plus wedge or segment	19	38	13	24.6	32	31.0
Without further therapy	(10)		(8)			
With prior thoracoplasty	(1)		(1)			
With concomitant thoracoplasty	(6)		(0)			
With subsequent thoracoplasty	(1)		(1)			
With prior and concomitant thoracoplasty	(1)		(2)			
With subsequent pneumoperitoneum	(0)		(1)			
Bilobectomy	0	0	1	1.9	1	1.0
Resection, type not stated	4	8	1	1.9	5	4.9
Without further therapy	(3)		(1)			
Concomitant thoracoplasty	(1)		(0)			
Thoracoplasty	2	4	3	5.6	5	4.9
Alexander type	(1)		(3)			
Plombage type	(1)		(0)			
No surgery	3	6	6	11.3	9	8.7
Total	50	100	53	100.0	103	100.0

25, 1950 (figure 8*A*) shows the maximum involvement by pulmonary tuberculosis. A bronchogram in the left anterior oblique view following treatment is shown for comparison (figure 8*B*). Recommendations for treatment are tabulated in table 8.

Recommendations by consultants: It may be seen that the surgeons and internists were in close agreement on the necessity for resection in tuberculosis associated with bronchiectasis. Some type of excision was agreed upon by 90 per cent of the surgeons and by 83.1 per cent of internists. Only 2 of 50 surgeons and 3 of 53 internists favored a primary thoracoplasty. Twenty surgeons (40 per cent) and 14 internists (26.5 per cent), however, advised a thoracoplasty as an adjunct to the resection. Three surgeons and 6 internists (8.7 per cent of all of the consultants) recommended only medical treatment, as the sputum had been negative for tubercle bacilli for nineteen months prior to consideration.

Operative findings: Dense pleural adhesions combined with nodular disease throughout all lobes caused the present writers to perform a right pneumonectomy. Bronchiectasis was marked in the right upper lobe and in the superior segment of the lower. The lower lobe contained numerous caseous areas surrounded by fibrous connective tissue. Acid-fast organisms were not demonstrated in the resected specimen.

Case 9. R. A. M., a 40-year-old white male, had a history of recurring tuberculous cavitation in the right lower lobe of seven years' duration (figure 9). Cavity closure did not occur

TABLE 9

SUGGESTED TREATMENT OF LOWER LOBE CAVITY

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Segmental resection	11	22	15	28.3	26	25.2
Without further therapy	(11)		(14)			
With postoperative pneumoperitoneum	(0)		(1)			
Lobectomy	33	66	26	49.1	59	57.3
Without further therapy	(31)		(22)			
After further drug therapy	(1)		(4)			
With insertion of prosthesis	(1)		(0)			
Resection, type not stated	6	12	9	17.0	15	14.6
No surgery	0		3	5.6	3	2.9
Total	50	100	53	100.0	103	100.0

with phrenic nerve crush or pneumoperitoneum. Chest roentgenograms obtained before and after pneumoperitoneum are presented for comparison (figure 9*A* and *B*). The patient's sputum became negative for tubercle bacilli after one month of a four-month course of streptomycin-PAS therapy. The patient's strain of *M. tuberculosis* was still inhibited by the drugs at the time he was considered for surgery.

Recommendations by consultants: There was agreement with respect to excisional therapy in this case (table 9) except for 3 of 53 internists (3 per cent of the entire group) who did not recommend resection. Lobectomy was the treatment of choice by 66 per cent of the surgeons and 49.1 per cent of the internists. One surgeon and 4 internists advised further drug therapy before lobectomy. Thoracoplasty was not advised either as primary treatment or in conjunction with pulmonary resection. One surgeon stated that he would use a prothesis at the time of lobectomy.

Operative findings: At the time of thoracotomy the lesion was sufficiently localized to warrant segmental resection. The excised 3 cm. cavity had a thick fibrous wall and communicated with two basal segmental bronchi. Acid-fast organisms were demonstrated in the resected specimen. The postoperative course was uneventful.

Case 10. R. F. G., a 46-year-old Negro male, had giant, thin-walled cavities in the right upper and middle lobes associated with sputum positive for tubercle bacilli. His strain of tubercle bacilli was resistant to streptomycin and PAS. He was unable to tolerate isoniazid, pyrazinamide, or viomycin because of liver impairment or allergic reaction. The chest roentgenograms in postero-anterior and right lateral positions (figure 10*A* and *B*) show the two cavitary lesions present eleven years after onset of pulmonary tuberculosis. These lesions had not changed in the five years preceding the present evaluation except for some fluctuation in size of the cavities. A spread of the disease in both midlung fields in 1946 had healed, as may be noted on the roentgenogram (figure 10*A*) by the small calcified densities in these areas.

Recommendations by consultants: Pulmonary resection was recommended (table 10) by the majority of both surgeons (94 per cent) and internists (92.3 per cent).

TABLE 10

SUGGESTED TREATMENT OF A PATIENT WITH BILOBAR CAVITATION AND SPUTUM POSITIVE FOR TUBERCLE BACILLI AND DRUG-RESISTANT

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Segmental resection	0		3	5.8	3	2.9
Without further therapy			(2)			
After needle aspiration of tension cavity			(1)			
Lobectomy plus wedge or segment	7	14	0		7	6.9
Without further therapy	(3)					
With concomitant thoracoplasty	(1)					
With subsequent thoracoplasty	(3)					
Bilobectomy	12	24	17	32.7	29	28.5
Without further therapy	(6)		(6)			
After further drug therapy	(0)		(1)			
With prior Alexander thoracoplasty	(1)		(1)			
With prior plombage thoracoplasty	(1)		(0)			
With concomitant thoracoplasty	(4)		(4)			
After further drug therapy	(0)		(1)			
With subsequent thoracoplasty	(0)		(4)			
Bilobectomy plus segment	3	6	1	1.9	4	3.9
Without further therapy	(0)		(1)			
With prior thoracoplasty	(1)		(0)			
With concomitant thoracoplasty	(2)		(0)			
Pneumonectomy	22	44	25	48.1	47	46.1
Without further therapy	(11)		(14)			
After further drug therapy	(0)		(4)			
After further drug therapy and pneumoperitoneum	(0)		(1)			
With prior thoracoplasty	(1)		(1)			
With prior and concomitant thoracoplasty	(1)		(0)			
After further drug therapy	(1)		(0)			
With concomitant thoracoplasty	(5)		(2)			
With subsequent Alexander thoracoplasty	(0)		(1)			
After further drug therapy	(0)		(1)			
Plus phrenic nerve crush	(0)		(1)			
With subsequent plombage thoracoplasty	(2)		(0)			
With insertion of prosthesis	(1)		(0)			
Resection, type not stated	3	6	2	3.8	5	4.9
Cavernostomy and concomitant thoracoplasty	1	2	0		1	1.0
Thoracoplasty						
Alexander type	2	4	1	1.9	3	2.9
No surgery	0		3	5.8	3	2.9
Total	50	100	52	100.0	102	100.0

As would be expected in a case of this type, however, there was some difference of opinion on how much to resect. It is obvious that the question of conserving pulmonary tissue could not be adequately settled before thoracotomy. The largest group were in favor of pneumonectomy, this recommendation being made

by 44 per cent of the surgeons and by 48.1 per cent of the internists. Excision of the upper and middle lobes plus the superior segment of the lower lobe was preferred by 3 surgeons (6 per cent) and by one internist (1.9 per cent). Removal of upper and middle lobes was recommended by 12 of 50 surgeons (24 per cent) and by 17 of 52 internists (32.7 per cent). Removal of less than two lobes was considered by 14 per cent of the surgeons and by 5.8 per cent of the internists. Thoracoplasty as a definitive treatment was recommended by 2 surgeons and one internist. As an adjunct to pulmonary resection, thoracoplasty was advised by 23 surgeons (46 per cent) and 16 internists (30.8 per cent). Further treatment with antituberculous drugs before excisional therapy was preferred by one surgeon and 9 internists. One surgeon stated that he would do a cavernostomy and concomitant thoracoplasty. Only 3 internists (2.9 per cent of total group) did not advise surgery.

Operative findings: Since it was believed that conservation of pulmonary tissue was important in this case, the right upper and middle lobes, together with the superior segment of the lower lobe, were removed. Along the pleural surface of the two large cavities, the walls were fused with the pleura and endothoracic fascia so that their removal was associated with pleural contamination. The remaining lung did not completely fill the pleural space following resection. The resulting mixed empyema, soon followed by bronchopleural fistula, necessitated an open thoracotomy on the fourteenth postoperative day. The patient did not tolerate this infection, his wounds did not heal, and he died on the twenty-seventh postoperative day.

Case 11. A. G. H., a 33-year-old Negro male, was considered to have a destroyed left lung. The first chest roentgenogram (figure 11*A*) was taken twenty-seven months after onset of pulmonary tuberculosis. Very little clearing in the left lung during the following eleven months was noted (film dated June 22, 1953, figure 11*B*) while the patient received streptomycin-PAS therapy with pneumoperitoneum. Even though there was bacterial susceptibility, the sputum was still positive for tubercle bacilli. Bronchoscopic evidence of old endobronchial disease was seen in each upper lobe orifice at the time he was considered for surgery.

Recommendations by consultants: Pneumonectomy was the most frequent recommendation, as was suggested by 41 of 50 surgeons (82 per cent) and by 38 of 53 internists (71.7 per cent). Thorocoplasty as an adjunct to pneumonectomy was recommended by 16 surgeons (32 per cent) and by 15 internists (28.3 per cent). Two surgeons recommended filling the remaining thorax after pneumonectomy with some type of prothesis. Thoracoplasty as the definitive treatment was suggested by 5 surgeons (10 per cent) and 6 internists (11.3 per cent). Of those who advised pneumonectomy, 5 surgeons and 15 internists recommended further drug therapy before surgery. In addition to further drug therapy, one of each group advised continuance of pneumoperitoneum. All surgeons considered surgical therapy while 6 internists did not advise surgical treatment.

Operative findings: An extrapleural left pneumonectomy was the choice of treatment by the present writers. A post-resection thoracoplasty for a bronchopleural fistula with empyema was performed seven weeks after pneumonectomy. The

TABLE 11

SUGGESTED TREATMENT OF A PATIENT WITH DESTROYED LUNG AND SPUTUM POSITIVE FOR TUBERCLE BACILLI

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Lobectomy	2	4	0		2	1.9
Pneumonectomy	41	82	38	71.7	79	76.7
Without further therapy	(19)		(12)			
After further drug therapy	(3)		(10)			
Plus pneumoperitoneum	(1)		(1)			
With prior thoracoplasty	(5)		(5)			
After further drug therapy	(1)		(0)			
With prior and concomitant thoracoplasty	(0)		(1)			
With prior and subsequent thoracoplasty	(1)		(0)			
With concomitant thoracoplasty	(4)		(3)			
After further drug therapy	(0)		(2)			
With subsequent thoracoplasty	(5)		(3)			
After further drug therapy	(0)		(1)			
With insertion of prosthesis	(2)		(0)			
Resection, type not stated	2	4	3	5.7	5	4.9
Without further therapy	(1)		(2)			
After further drug therapy	(1)		(1)			
Thoracoplasty, Alexander type	5	10	6	11.3	11	10.7
Without further therapy	(5)		(5)			
With concomitant pneumoperitoneum	(0)		(1)			
No surgery	0		6	11.3	6	5.8
Total	50	100	53	100.0	103	100.0

resected lung revealed nodular disease in both lobes, an 8 cm. cavity in the apical-posterior segment and a 5 cm. cavity in the anterior basal segment of the left lower lobe. In addition, there were large dilated bronchial structures, considered to be congenital in origin. Acid-fast organisms were demonstrated in the resected tissues. The postoperative course following thoracoplasty was uneventful.

Case 12. R. McM. In this 33-year-old Negro male, a left pyopneumothorax was present, associated with a bronchopleural fistula, spread of disease to the contralateral lung, and moderate shift of the mediastinum (figure 12*A*). As may be seen by the abstracted history (figure 12), the intrapleural infection was treated by repeated thoracentesis with intrapleural injections of penicillin and streptomycin. A closed thoracotomy was performed after admission to the hospital. This was followed by an open thoracotomy nine days later. The patient's strain of tubercle bacilli had become resistant to streptomycin and to PAS. The sputum was still positive for tubercle bacilli and endobronchial disease was seen in the basal segments of the left lower lobe on bronchoscopy. The patient had received chemotherapy (isoniazid-streptomycin-PAS) for four months before consideration for further surgical treatment. A chest roentgenogram obtained at this time is shown (figure 12*B*, dated January 4, 1954) for comparison with the earlier film. The open thoracotomy tract may still be seen at the left base.

Recommendations by consultants: Pneumonectomy was considered the procedure of choice by the majority of surgeons (82 per cent) and internists (79.2 per

TABLE 12

SUGGESTED TREATMENT OF DESTROYED LUNG WITH BRONCHOPLEURAL FISTULA AND OPEN THORACOTOMY

Treatment	Surgeons		Internists		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Lobectomy	1	2.0	2	3.8	3	2.9
Without further therapy	(1)		(0)			
With decortication of lower lobe	(0)		(1)			
After further drug therapy	(0)		(1)			
Pneumonectomy	41	82.0	42	79.2	83	80.6
Without further therapy	(15)		(18)			
After further drug therapy	(0)		(2)			
With prior thoracoplasty	(3)		(5)			
With prior and concomitant thoracoplasty	(3)		(1)			
With prior and subsequent thoracoplasty	(1)		(0)			
With concomitant thoracoplasty	(9)		(10)			
With subsequent thoracoplasty	(10)		(5)			
After further drug therapy	(0)		(1)			
Resection, type not stated	2	4.0	2	3.8	4	3.9
Without further therapy	(1)		(1)			
With concomitant thoracoplasty	(0)		(1)			
With concomitant thoracoplasty and closure bronchopleural fistula	(1)		(0)			
Thoracoplasty	5	10.0	4	7.5	9	8.7
Alexander type	(5)		(3)			
Schede type	(0)		(1)			
No surgery	1	2.0	3	5.7	4	3.9
Total	50	100.0	53	100.0	103	100.0

cent). Lobectomy was preferred by one surgeon. Lobectomy plus decortication of the lower lobe was advised by 2 internists. Resection, type not stated, was recommended by 2 of each group. Five surgeons (10 per cent) and 4 internists (7.5 per cent) recommended a thoracoplasty as the definitive treatment. At some time in conjunction with pulmonary resection, thoracoplasty was advised by 27 surgeons (54 per cent) and 23 internists (43.4 per cent). Four internists advised further drug therapy before pulmonary resection. One surgeon was optimistic enough to suggest pulmonary resection with concomitant thoracoplasty and closure of the bronchopleural fistula. A more pessimistic view was expressed by one surgeon and 3 internists who did not advise surgery.

Operative findings: A two-stage, eight-rib Alexander type of thoracoplasty was performed following the second chest roentgenogram shown in figure 12*B*. Due to the continued presence of tubercle bacilli in the sputum and a bronchopleurocutaneous fistula, a left pneumonectomy was performed six months after thoracoplasty. A third stage of thoracoplasty, including the ninth rib, was performed three months after pneumonectomy to close the residual pleural space. The resected lung revealed a 2 cm. apical cavity and caseous nodular disease throughout the upper lobe and upper two-thirds of the lower lobe. Acid-fast

organisms were demonstrated in the resected tissue. The postoperative course was uneventful following the last operative procedure.

SUMMARY

A study was made to determine whether there is a reasonable unanimity of opinion as to the place of surgery in the therapy of pulmonary tuberculosis. Representative roentgenograms and an abstract of the clinical history of 12 patients who have undergone surgery at Oteen were sent to 50 thoracic surgeons and 53 thoracic internists. These consultants were asked to recommend a type of treatment for each patient and to base the selection upon the philosophy of treatment held today rather than at the time of the last film.

Pulmonary resection has definitely become accepted as a method of treatment for pulmonary tuberculosis. In the present study, the internist has recommended pulmonary resection almost as frequently as the surgeon. Pulmonary resection was suggested ten times more frequently than primary thoracoplasty.

In general, thoracoplasty has shifted in its importance as a definitive treatment of pulmonary tuberculosis to a role of being an adjunct to pulmonary resection. This type of thoracoplasty was suggested two and a half times more frequently than was thoracoplasty alone, as was noted in cases with larger cavities and destroyed lung (*Cases 6, 7, 11*, and *12*).

Nodules and cavities, 2.5 cm. or greater in size, as well as bronchiectasis associated with tuberculosis, are apparently accepted as clear indications for resection (*Cases 1, 2, 3, 4, 5*, and *8*).

SUMARIO

Repaso en Gran Escala a Estilo de Jurado de las Indicaciones de la Cirugía en la Tuberculosis Pulmonar

En este estudio, tratóse de determinar si existía bastante unanimidad en cuanto al puesto de la cirugía en la terapéutica de la tuberculosis pulmonar. A 50 cirujanos torácicos y a 53 internistas torácicos se les enviaron típicas radiografías y un sumario de la historia clínica de 12 enfermos que se habían sometido a la cirugía en le Sanatorio de Oteen. A esos consultores se les pidió que recomendaran una forma de tratamiento para cada enferomo, basando su selección en los conceptos del tratamiento que reinan hoy día más bien que en los de la época de la última radiografía.

La resección pulmonar ha sido ya definitivamente aceptada como método de tratamiento para la tuberculosis pulmonar. En el estudio actual, obsérvase que el internista ha recomendado esa operación con la misma frecuencia que el cirujano. La resección pulmonar fué propuesta diez veces más a menudo que la toracoplastia primaria.

En general, la toracoplastia ha girado en su importancia, de tratamiento definitivo de la tuberculosis pulmonar al papel de coadyuvante de la resección pulmonar. Esta forma de toracoplastia fué propuesta dos y media veces más a menudo que la toracoplastia sola, según se notó en los casos con cavernas mayores y destrucción del pulmón (casos 6, 7, 11 y 12).

Los nódulos y las cavernas, de 2.5 cm. o más de tamaño, así como la bronquiectasia asociada con tuberculosis, se aceptan aparentemente como indicaciones explícitas de la resección (casos 1, 2, 3, 4, 5 y 8).

RESUME

Compte-rendu, type consensus, des indications chirurgicales dans la tuberculose pulmonaire

Il a été procédé à une enquête pour déterminer s'il existait une certaine unanimité d'opinion sur la place de la chirurgie dans le traitement de la tuberculose pulmonaire. Des

radiogrammes caractéristiques et un résumé des antécédents cliniques concernant 12 malades, qui avaient été soumis à l'intervention chirurgicale à l'hôpital d'Oteen, ont été envoyés à 50 spécialistes de la chirurgie thoracique et à 53 médecins spécialistes des maladies du poumon. Ces consultants ont été priés d'indiquer le traitement qu'ils préconiseraient pour chaque malade, en basant leur choix d'après les conceptions actuelles de préférence à celles qui étaient acceptées au moment de la prise du dernier cliché.

La résection pulmonaire est maintenant définitivement acceptée comme méthode de traitement de la tuberculose pulmonaire, le médecin recommande la résection pulmonaire presque aussi fréquemment que le chirurgien. La résection pulmonaire a été proposée dix fois plus fréquemment que la thoracoplastie primaire.

En général, la thoracoplastie a perdu de son importance comme traitement définitif de la tuberculose pulmonaire, elle est passée au rôle d'auxiliaire de la résection pulmonaire. Cette chirurgie d'exérèse a été suggérée deux fois et demi plus souvent que la thoracoplastie seule, comme on l'a constaté dans les cas avec cavernes importantes et destruction du poumon (cas 6, 7, 11 et 12).

Les lésions nodulaires et les excavations, dont les dimensions atteignaient ou dépassaient 2.5 cm. ainsi que les bronchiectasies associées à la tuberculose, sont apparemment acceptées comme des indications nettes de résection (cas 1, 2, 3, 4, 5 et 8).

FIGURES 1–12

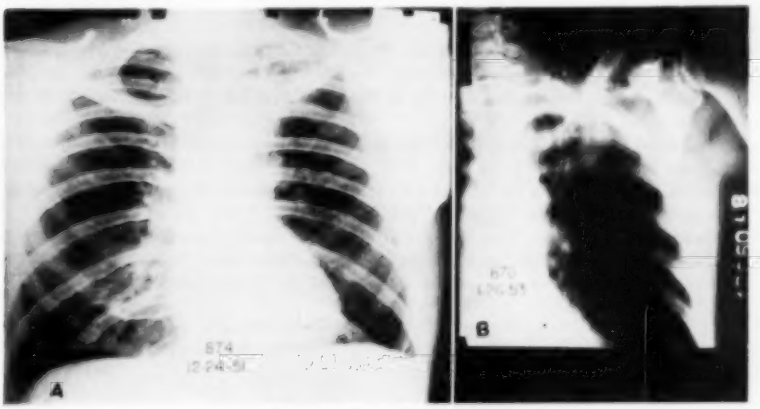

FIG. 1. *Case 1* (R.T.S.)

48-year-old white male.

Onset of disease: December, 1951.

Treatment: Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily, from March 3, 1952 to March 11, 1953.

Resistance studies: September 2, 1952. Drug susceptibility to patient's strain of tubercle bacilli inhibited by: streptomycin concentrations of less than 10 γ per ml.; PAS concentrations, less than 10 γ per ml.

Sputum, positive for tubercle bacilli by culture for the last time on September 2, 1952.

Bronchoscopy, negative on March 2, 1953.

Course: Onset of disease was in December, 1951, with "viral" pneumonia. Diagnosis of tuberculosis was made on January 4, 1952.

A. Chest roentgenogram dated December 24, 1951, showing tuberculosis in left apex at onset.

B. Planigram dated January 26, 1953, revealing a 1.5 cm. inspissated cavity at level of third rib posteriorly. Sputum was negative for *M. tuberculosis*. Bacterial susceptibility was present. Opinion for resectional and medical treatment was equally divided.

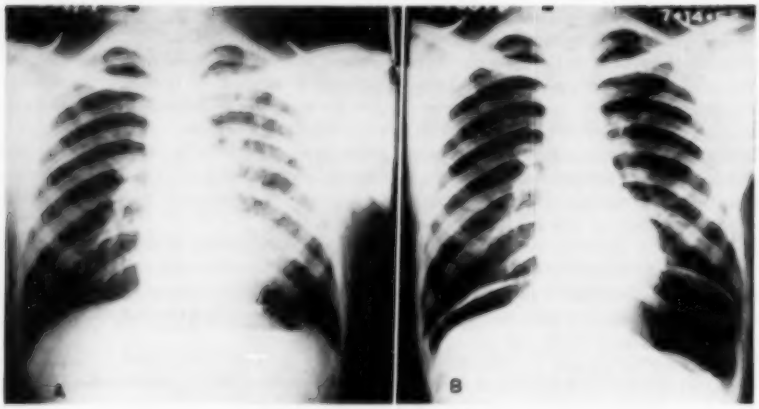

FIG. 2. *Case 2* (W.C.)

28-year-old Negro male.

Onset of disease: July, 1951.

Treatment:

Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily, from September 14, 1951 to July 14, 1952.

Pneumoperitoneum, September 21, 1951 to July 14, 1952.

Resistance studies: None.

Sputum, positive for tubercle bacilli for the last time on September 21, 1951.

Bronchoscopy, negative on July 24, 1952.

A. Maximum involvement by tuberculosis in left lung one month after onset is shown in roentgenogram dated August 31, 1951.

B. Second roentgenogram, obtained on July 14, 1952, reveals a residual 3 cm. cavity beneath the clavicle. Sputum was negative for *M. tuberculosis*. Bacterial susceptibility was present. Pulmonary resection was advised by 76 per cent of combined group.

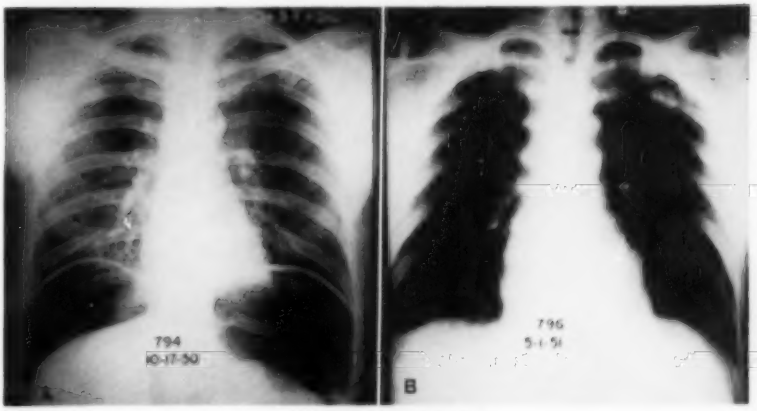

FIG. 3. *Case 3* (W.O.D.)

31-year-old white male.

Onset of disease: February, 1950.

Treatment:

Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily, from April 10 to May 1, 1951.
Pneumoperitoneum, September 5, 1950, to April 17, 1951.

Resistance studies: May 1, 1951. Drug susceptibility to patient's strain of tubercle bacilli inhibited by streptomycin concentrations of less than 10 γ per ml.

Sputum, positive for tubercle bacilli by culture for the last time on May 1, 1951.

Bronchoscopy, negative on April 23, 1951.

Course: No drug therapy was given this patient other than that noted above. The lesion in the right upper lobe revealed no evidence of cavitation on planigrams obtained on May 1, 1951.

A. Bilateral apical nodules eight months after onset of tuberculosis are shown in the roentgenogram dated October 17, 1950.

B. Planigram obtained on May 1, 1951, reveals a small nodule in the left fourth posterior interspace. Sputum was positive for tubercle bacilli. Bacterial susceptibility was present. Pulmonary resection, left, was recommended by 92 per cent of the combined group.

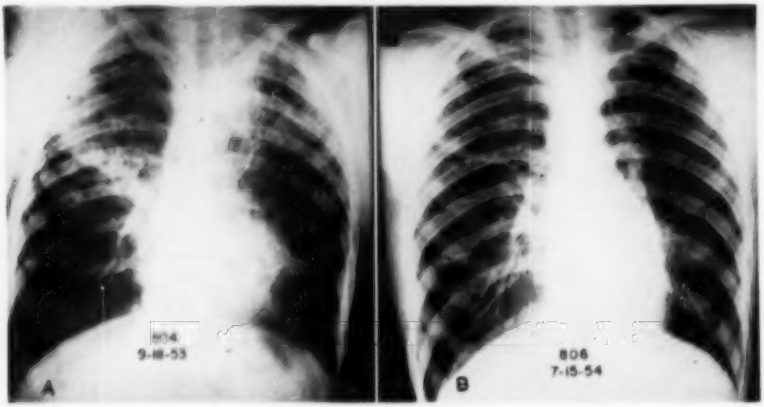

FIG. 4. *Case 4* (C.E.P.)

19-year-old white male.

Onset of disease: July, 1953.

Treatment: Streptomycin, 1 gm. twice weekly; isoniazid, 300 mg. daily, from September 28, 1953 to July 30, 1954.

Resistance studies: December 3, 1954. Drug susceptibility to patient's strain of tubercle bacilli inhibited by streptomycin in concentrations of less than 10 γ per ml.

Sputum, positive for tubercle bacilli by culture for the last time on February 10, 1954.

Bronchoscopy, negative on July 2, 1954.

Course: Continued improvement in bilateral pulmonary disease except for cavitation in left apex. Planigrams of right lung were reported to be negative.

A. Bilateral tuberculosis two months after onset may be seen on the first roentgenogram, dated September 18, 1953.

B. Second film, obtained on July 15, 1954, shows a so-called "isoniazid" cavity in left apex. Sputum was negative for tubercle bacilli. Bacterial resistance to streptomycin was present. Pulmonary resection was the treatment recommended by 88 per cent of the combined group.

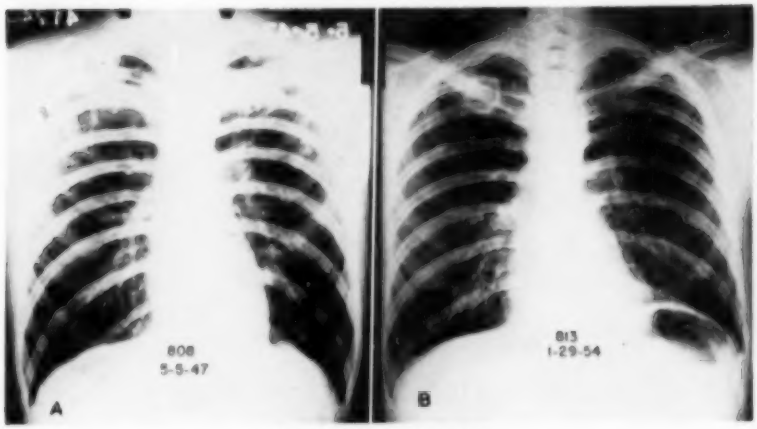

FIG. 5. *Case 5* (W.G.S.)

33-year-old white male.

Onset of disease: January, 1947.

Treatment:

Streptomycin, 1 gm. twice weekly; PAS, 12 gm, daily, from September 9, 1952 to July 3, 1953.

Streptomycin, 1 gm. twice weekly; isoniazid, 300 mg. daily, from July 25, 1953 to January 29, 1954.

Pneumoperitoneum, May, 1947 to July, 1951.

Phrenic nerve crush, left, May, 1947.

Resistance studies: December 14, 1953. Drug susceptibility to patient's strain of tubercle bacilli inhibited by: streptomycin concentrations of less than 10 γ per ml.; isoniazid concentrations of less than 10 γ per ml.

Sputum, positive for tubercle bacilli by microscopy for the last time on January 4, 1954.

Bronchoscopy, negative on January 28, 1954.

Course: Planigrams of left apex were reported negative for cavitation on January 11, 1954.

A. Bilateral apical cavitary disease four months after onset of tuberculosis is revealed by the first roentgenogram, obtained on May 5, 1947.

B. The second roentgenogram, dated January 29, 1954, shows a residual cavity in the right apex. Sputum was positive for tubercle bacilli. Partial resistance to drugs was present. Pulmonary resection was recommended as primary treatment by 93 per cent of the combined group.

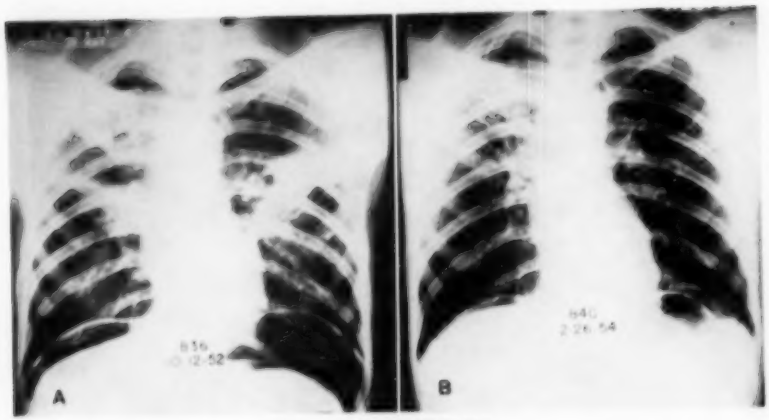

FIG. 6. *Case 6* (E.T.K.)

29-year-old white male.

Onset of disease: July, 1952.

Treatment:

Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily, from August 9, 1952 to August 26, 1952. (Patient was unable to take PAS due to nausea and diarrhea.)

Streptomycin, 1 gm. twice weekly, from August 27, 1952 to November 8, 1952.

Isoniazid, 150 mg. daily, from October 8, 1952 to October 15, 1952.

Isoniazid, 300 mg. daily; streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily from November 12, 1952 to November 4, 1953 (discontinued due to resistance to these drugs).

Viomycin, 1 gm. weekly, from November 5, 1953 to January 26, 1954 (discontinued due to resistance to drugs).

Pneumoperitoneum, September 29, 1952 to January 25, 1954.

Resistance studies: November 9, 1953. Drug susceptibility to patient's strain of tubercle bacilli inhibited by: streptomycin concentrations of 10 γ per ml.; PAS concentrations of 100 γ per ml.; isoniazid concentrations of 5 γ per ml.; and viomycin concentrations of 50 γ per ml.

Sputum, positive for tubercle bacilli by culture and microscopy for the last time on November 6, 1953.

Bronchoscopy, negative on February 15, 1954.

Course: Spread of disease occurred bilaterally during streptomycin therapy in October, 1952. Planigrams on January 25, 1954, revealed no evidence of cavitation in left lung. Patient has had no drug therapy since January 26, 1954.

A. Bilateral tuberculosis four months after onset is shown in first film, dated October 12, 1952.

B. Second roentgenogram dated February 26, 1954, reveals residual disease in right upper lobe. A cavity was present on planigraphic study. Sputum was negative for tubercle bacilli. Complete drug resistance was present. The treatment advised by 63 per cent of the combined group was pulmonary resection and thoracoplasty by 33 per cent.

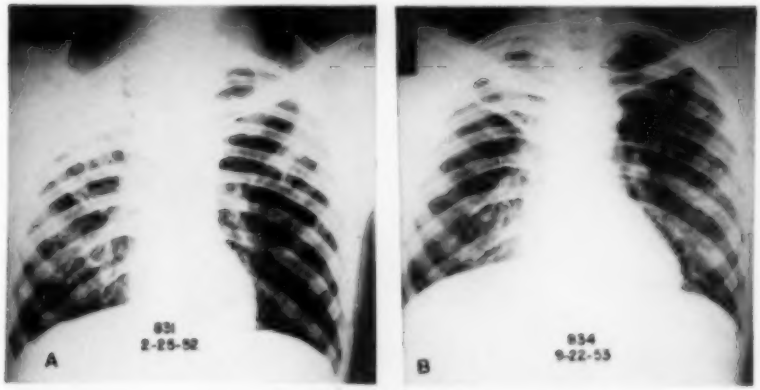

FIG. 7. *Case 7* (O.E.B.)

37-year-old Negro male.

Onset of disease: August, 1950.

Treatment:

Streptomycin, 1 gm. daily; PAS, 12 gm. daily, from October 20, 1950 to April 13, 1951.

Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily, from February 26, 1952 to March 3, 1952, and from March 4, 1952 to June 3, 1952.

Isoniazid, 150 mg. daily, from March 4, 1952 to June 3, 1952.

Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily, from June 4, 1952 to July 31, 1952.

Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily, November 4, 1952 to September 22, 1953.

Pneumoperitoneum, December, 1950 to December, 1951.

Resistance studies: July 10, 1953. Drug susceptibility to patient's strain of tubercle bacilli inhibited by: streptomycin concentrations of 100 γ per ml.; PAS concentrations of 100 γ per ml.; isoniazid concentrations of 1 γ per ml.

Sputum, positive for tubercle bacilli by culture for the last time on July 10, 1953.

Bronchoscopy, negative on September 21, 1953.

Course: Bilateral spread of disease occurred in February, 1952. No evidence of cavitation was present in the left lung on the planigrams dated August 18, 1953.

A. A spread to right lower- and left midlung fields is present in the first film, dated February 25, 1952.

B. Clearing of this spread is shown in the second film, dated September 22, 1953. Sputum was positive for tubercle bacilli. Resistance to streptomycin and PAS was present. The treatment recommended by 84 per cent of the entire group was pulmonary resection; 16 per cent of the combined group recommended thoracoplasty.

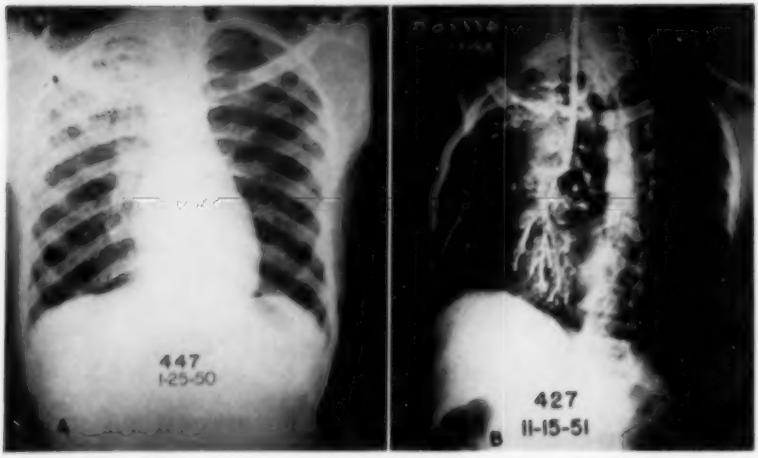

FIG. 8. *Case 8* (O.J.)

29-year-old Negro male.

Onset of disease: March, 1949.

Treatment: Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily, from May 5, 1950 to December 14, 1951; no collapse therapy.

Resistance studies: None available.

Sputum, positive for tubercle bacilli for the last time in May, 1950.

Bronchoscopy, negative on November 1, 1951.

Course: Planigrams of right apex in October, 1951, revealed no evidence of cavitation other than that considered to be bronchiectatic dilatations.

A. Maximum involvement by pulmonary tuberculosis is noted on the first roentgenogram, dated January 25, 1950.

B. The bronchogram in left anterior oblique view shows bronchiectasis in right upper lobe and superior segment of right lower lobe. The sputum was negative for tubercle bacilli. The treatment recommended by 86 per cent of both groups was pulmonary resection.

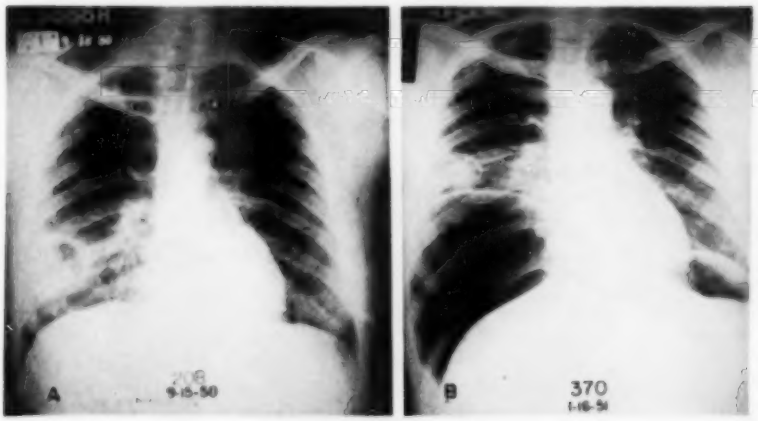

FIG. 9. *Case 9* (R.A.M.)

40-year-old white male.

Onset of disease: August, 1943.

Treatment:

Streptomycin, 1 gm. daily; PAS, 12 gm. daily, from September 19, 1950 to January 16, 1951.

Phrenic nerve crush, right, September 4, 1944 and August 28, 1945.

Pneumoperitoneum, October 17, 1950 to January 16, 1951.

Resistance studies: Drug susceptibility to patient's strain of tubercle bacilli inhibited by: streptomycin concentrations of 3.0 γ per ml.; PAS concentrations of 1.0 γ per ml.

Sputum, positive for tubercle bacilli by culture for the last time on October 20, 1950.

Bronchoscopy, negative on December 15, 1950.

Course: Chest roentgenogram on May 6, 1948, revealed evidence of cavitation in nodule in right lower lobe.

A. and *B*. Roentgenograms obtained before and during pneumoperitoneum used in treatment of this right lower lobe tuberculous cavity. Sputum was negative for tubercle bacilli. Bacterial susceptibility was present. Pulmonary resection was preferred by 97 per cent of the entire group.

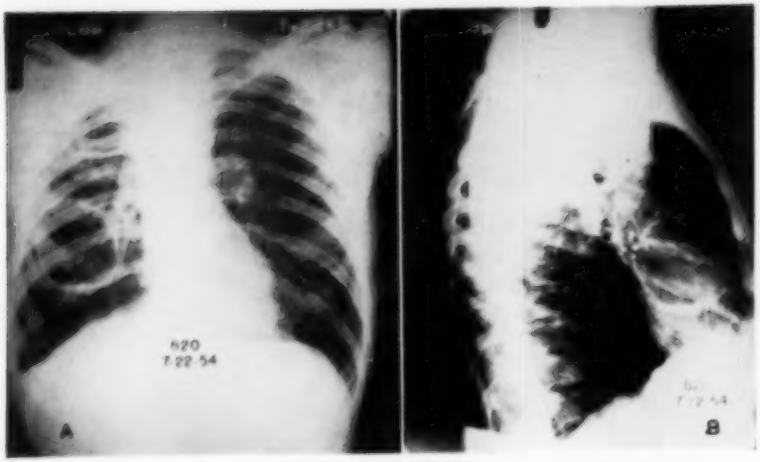

FIG. 10. *Case 10* (R.G.)

46-year-old Negro male.

Onset of disease: In 1943.

Treatment:

Streptomycin, 1 gm. weekly; PAS, 12 gm. daily, from June, 1949 to September, 1949.

Streptomycin, 1 gm. weekly, from April, 1951 to August, 1951.

Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily, from April 11, 1952 to July 1, 1952.

Isoniazid, 300 mg. daily; pyrazinamide, 3 gm. daily, from August 30, 1953 to January 25, 1954. Discontinued because of jaundice.

Viomycin, 1.0 gm. twice weekly; oxytetracycline, 2.0 gm. daily, from April 30, 1954 to June 14, 1954. Discontinued because of dermatitis, generalized.

Resistance studies: June 16, 1954. Drug susceptibility to patient's strain of tubercle bacilli inhibited by: streptomycin concentrations of 10 γ per ml.; PAS concentrations of 100 γ per ml.; isoniazid concentrations of 1 γ per ml.

Sputum, positive for tubercle bacilli by culture for the last time on June 16, 1954.

Bronchoscopy, negative on June 16, 1954.

Course: Large cavities in right lung fluctuated in size from time to time, the most marked improvement being during treatment with isoniazid and pyrazinamide.

A. and *B.* Chest roentgenograms in two views, on July 22, 1954, were taken eleven years after onset of tuberculosis. Drug resistance or drug intolerance was present to most antituberculous drugs. Sputum was positive for tubercle bacilli. Pulmonary resection was recommended by 92 per cent of total group.

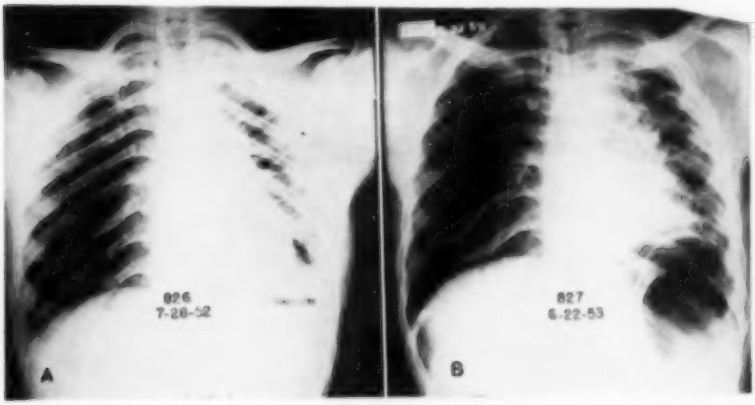

FIG. 11. *Case 11* (A.H.)

33-year-old Negro male.

Onset of disease: April, 1950.

Treatment:

Streptomycin, 1 gm. daily; PAS, 12 gm. daily, from May 18, 1950 to September 11, 1950.

Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily, from July 2, 1952 to September 4, 1953.

Pneumoperitoneum, March 18, 1953 to June 22, 1953.

Resistance studies: December 15, 1952. Drug susceptibility to patient's strain of tubercle bacilli inhibited by streptomycin concentrations of less than 10 γ per ml.

Sputum, positive for tubercle bacilli by microscopy of concentrate for the last time on June 22, 1953.

Bronchoscopy, June 17, 1953. Evidence of old endobronchial disease present in right upper and left upper lobe orifices, appearing to be more active on right.

A. First roentgenogram, obtained on July 28, 1952, was taken twenty-seven months after onset of tuberculosis.

B. Second film shows improvement with treatment by June 22, 1953. Sputum was positive for tubercle bacilli. Bacterial susceptibility was present. Pulmonary resection was recommended by 84 per cent of surgeons and internists. Thoracoplasty was advised by 11 per cent of the group.

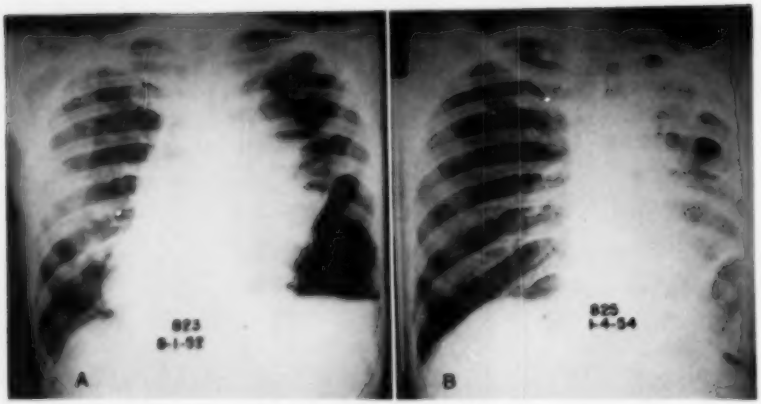

FIG. 12. *Case 12* (R.McM.)

33-year-old Negro male.

Onset of disease: April, 1952.

Treatment:

Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily, from June 4, 1952 to September 12, 1953.

Streptomycin, 1 gm. twice weekly; PAS, 12 gm. daily; isoniazid, 300 mg. daily, from September 13, 1953 to January 4, 1954.

Thoracentesis, repeated, left, June, 1952 to May, 1953, with injection of streptomycin and penicillin on each occasion.

Pneumoperitoneum, February 7, 1953 to June 16, 1953.

Closed thoracotomy, left, July 12, 1953.

Open thoracotomy, left, July 21, 1953.

Resistance studies: December 5, 1953. Drug susceptibility to patient's strain of tubercle bacilli inhibited by streptomycin concentrations of 100 γ per ml.; PAS concentrations of 100 γ per ml.; isoniazid concentrations of 1 γ per ml.

Sputum, positive for tubercle bacilli on microscopy for the last time on January 4, 1954.

Bronchoscopy, June 22, 1953. Endobronchial disease in basal segments of left lower lobe.

Course: Spontaneous pneumothorax, left base, developed in July, 1952. Definite bronchopleural fistula was diagnosed on June 29, 1953, by expectoration of dye from pleural cavity. Tuberculous empyema in left base was confirmed by culture.

A. First roentgenogram, dated August 1, 1952, shows left pyopneumothorax associated with bronchopleural fistula and spread of tuberculosis to contralateral lung. Onset was in April, 1952.

B. Film, obtained on January 4, 1954, shows improvement after left open thoracotomy and chemotherapy. Sputum was positive for tubercle bacilli. Endobronchial disease was present. Acid-fast bacteria were resistant to streptomycin and PAS. Left pneumonectomy was advised by 81 per cent of the group. Thoracoplasty was recommended by 9 per cent.

HINCONSTARCH IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

Report on Pilot Investigation

VINCENT C. BARRY, MICHAEL L. CONALTY, HENRY E. COUNIHAN, AND BRENDAN O'BRIEN

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INTRODUCTION

Hinconstarch is a polymer prepared from periodate-oxidized potato starch by condensation with equimolar proportions of isoniazid and *p*-aminobenzalthiosemicarbazone (1–3). It is a yellow amorphous powder insoluble in water and, accordingly, its antituberculosis activity *in vitro* was not investigated. Hinconstarch showed high activity in mice and guinea pigs infected with tubercle bacilli susceptible or resistant to isoniazid, and its toxicity for mice is very low (4). In the light of these facts, it was considered that hinconstarch merited investigation in human tuberculosis.

The pilot trial reported here was designed to examine the therapeutic efficiency of hinconstarch in pulmonary tuberculosis, to establish the appropriate dosage, and to study the emergence of isoniazid-resistant bacilli in hinconstarch-treated patients.

PLAN OF INVESTIGATION

Selection of Patients

For the purposes of the pilot trial, such patients were accepted as would ordinarily be treated with the usual multiple-drug regimens made up of streptomycin, isoniazid, or para-aminosalicylic acid (PAS) provided they had such clinical, bacteriologic, and roentgenographic signs as would enable changes during treatment to be readily assessed. It was a condition of acceptance in this pilot investigation that the tubercle bacilli isolated from each patient should be isoniazid-susceptible. It happened that none of the patients selected had had previous chemotherapy for tuberculosis.

The first 9 suitable patients who were admitted to the tuberculosis unit of the Meath Hospital were accepted for trial. Three other patients were accepted in St. Laurence's Hospital. Thus, in all, there were 12 patients (8 male, 4 female), with ages ranging from thirteen and one-half to fifty-nine years.

In accordance with the 1950 classification of the National Tuberculosis Association, *Patients Nos. 3, 5, 6, 7, 10,* and *11* were considered to have moderately advanced, and *Patients Nos. 1, 2, 4, 8, 9* and *12* far advanced, pulmonary tuberculosis.

Observation of Patients

Before the start of treatment, detailed clinical, laboratory, and roentgenographic studies were made of each patient. So as to detect any possible toxicity and to follow the progress of therapy, examinations and estimations were repeated at intervals as follows:

Fortnightly: Sputum microscopy and culture for tubercle bacilli; serum protein;

[1] From the Laboratories of the Medical Research Council of Ireland, St. Laurence's Hospital, and The Meath Hospital, Dublin, Ireland.

albumin-globulin ratio; Van den Bergh; thymol turbidity; alkaline phosphatase and blood urea.

Monthly: Body weight, erythrocyte sedimentation rate (Westergren, one hour), and roentgenogram of chest.

Monthly (more frequently if clinically indicated): Hemoglobin, erythrocyte, and leukocyte counts with differential count and packed cell volume.

Normally, direct drug-susceptibility tests were done with Löwenstein-Jensen tubes of medium containing 0, 0.2, 1.0, 5.0, and 25.0 γ of isoniazid per ml. With less than 15 colonies on either of the two control tubes of medium, however, an indirect drug-susceptibility test was done on the growth in the control tubes. Whenever a negative culture was obtained, subsequent attempts at isolation of bacilli from that patient were made on three tubes of medium (two plain and one containing 0.2 γ of isoniazid per ml.), an indirect test again being done in cases in which there were less than 15 colonies on a control tube and in all cases in which there was growth in the 0.2 γ per ml. tube. Whenever the patient was sputum free, laryngeal swabs were taken on three consecutive days for culture on three tubes as above.

All examinations made before treatment to establish the current status of the patients were repeated at the end of three months of hinconstarch therapy.

Hinconstarch Dosage

The drug was administered orally in 100 mg. gelatine capsules. Later, 200 mg. capsules were used. Initial dosage was 0.5 gm. daily but, as experience was gained, this was increased to 1.2 gm. daily and, in some cases, to 1.6 gm. daily, in three divided doses.

RESULTS

The course of the pulmonary tuberculosis in the 12 patients during hinconstarch therapy is presented in detail in tables 1 to 4, inclusive.

TABLE 1

CLINICAL FINDINGS AT START AND AFTER THREE MONTHS

Case Number	Age	Sex	General Physical Condition		Appetite		Weight		Cough*		Daily Sputum†		Temperature, °F.‡	
			Start	3 Months	Start	3 Months	Start	3 Months	Start	3 Months	Start	3 Months	Start	3 Months
							pounds	*pounds*			*cc.*	*cc.*		
1	32	F	Poor	Fair	Good	Good	99	109	3	tr.	30	tr.	98.6	97.5
2	24	M	Fair	Good	Good	Good	134	141	1	0	30	0	97.1	96.8
3	24	M	Fair	Good	Good	Good	129	143	1	0	15	0	97.6	97.9
4	20	M	Good	Good	Good	Good	157	172	0	0	tr.	tr.	97.2	97.0
5	13	M	Poor	Good	Good	Good	92	107	3	0	tr.	0	99.7	97.9
6	21	F	Good	Good	Good	Good	102	101	2	0	tr.	0	97.7	96.9
7	27	F	Fair	Good	Poor	Good	99	105	2	0	15	tr.	97.3	97.5
8	40	M	Good	Good	Good	Good	146	157	1	tr.	tr.	tr.	97.5	97.6
9	16	F	Good	Good	Poor	Good	102	115	2	0	15	tr.	102.2	97.4
10	37	M	Poor	Fair	Good	Good	134	148	2	tr.	30	tr.	97.4	98.0
11	53	M	Fair	Fair	Fair	Good	114	122	tr.	tr.	tr.	tr.	97.4	97.4
12	26	M	Fair	Good	Good	Good	147	154	2	2	15	15	97.4	97.4

* Graded from 3 (very severe) to 0

† Tr. = trace, i.e., on effort patient can cough up a little sputum for examination

‡ Average of seven consecutive evenings

TABLE 2

ERYTHROCYTE SEDIMENTATION RATE (WESTERGREN, ONE HOUR, 200 MM. SCALE)

Patient Number	1	2	3	4	5	6	7	8	9	10	11	12
Erythrocyte sedimentation rate at start	40	5	15	5	50	16	45	30	85	9	28	16
Erythrocyte sedimentation rate at three months	28	4	3	4	2	13	5	20	28	11	10	32

General Findings

General physical condition: As assessed at the start of treatment, only 4 patients were in good general condition with respect to state of nutrition and musculature; 5 were classified as fair, and 3 as poor (table 1). After three months, 9 were classified as good and 3 as fair. Of those 8 patients whose general condition was regarded as being poor or fair at the start, only one (*Patient No. 11*) was regarded as not having improved.

Appetite and weight: At the end of three months of hinconstarch therapy, appetite was good in all cases (table 1). It will be noted that all patients showed an increase in weight (mean increase of 9.9 pounds) with the exception of *Patient No. 6*, who was at her normal healthy weight throughout.

Cough and sputum: Cough which had been very troublesome in some cases, necessitating administration of codeine, responded rapidly to hinconstarch (table 1). At the end of the trial period, for all practical purposes, cough was ab-

TABLE 3

CHANGES IN ROENTGENOGRAPHIC APPEARANCES

Patient Number	Cavitation*		Extent of Infiltration†		Over-All Roentgenographic Improvement
	Start	3 Months	Start	3 Months	
1	4	4	4	3	Moderate
2	0	0	3	1	Marked
3	2	0	3	1	Marked
4	3	0	3	1	Marked
5	1	0	2	1	Moderate
6	3	20	2	2	Slight
7	3	2	2	2	Slight
8	2	0	2	1	Marked
9	0	0	3	3	Slight
10	1	0	3	2	Moderate
11	0	0	1	0	Cleared
12	2	1	2	2	Slight

* *Cavitation* 0 = None
1 = Smallest
2 = Moderate-sized single or 2 or 3 small
3 = Multiple small or single large
4 = Multiple large

† *Extent of infiltration:* Arbitrary scale ranging from small infiltration, 1, to very widespread involvement, 4

sent in all patients except *Patient No. 12*. Sputum was markedly decreased and only the last-named patient had a measurable amount.

Temperature: Initially, 2 patients had fever and, of these, one (*Patient 9*), who had acute tuberculous pneumonia, had marked pyrexia. All were afebrile at the end of the observation period (table 1).

Erythrocyte sedimentation rate (*Westergren*): The mean erythrocyte sedimentation rate for the group fell from 28.7 to 13.3 mm. Four patients continued to have sedimentation rates markedly outside the limits of normal but even these, with the exception of *Patient No. 12*, showed an improvement over their initial rates (table 2).

Roentgenographic Changes

There was roentgenographic improvement in all patients (table 3). One (*Patient No. 11*) showed complete roentgenographic clearing, 4 showed marked improvement, 3 moderate improvement, and 4 slight improvement. In *Patient No. 1* the improvement was more marked than can well be expressed in tabular form as, although the right lung remained in very bad condition, even there multiple large cavities became appreciably smaller. Disappearance of cavities was noted in *Patients Nos. 3*, *4*, *5*, *8*, and *10*, that is in 5 of the 9 patients who originally had cavities. In *Patient No. 6* the cavities were no longer clearly recognizable.

CASE REPORTS

Case 1. A 32-year-old woman (housekeeper) had a worsening cough for six months with copious greenish sputum. Her general condition was poor and remained poor on bed rest while awaiting treatment. On treatment there was a striking improvement in her physical condition although it could not yet be described as good. Sputum had practically disappeared. Her initial roentgenogram showed almost complete destruction of her right lung with numerous large cavities and also spread of the disease to the left lung. At the end of three months the cavities on the right side were appreciably smaller and the left lung was almost clear. A cavity 1 cm. in diameter in the left upper lobe had disappeared.

Case 2. Following hemoptysis, a 24-year-old man (boot repairer) was treated (phrenic crush) in a sanatorium during 1944–1945. After a further sanatorium period of seven months in 1949, he remained well until December, 1954, when he had another hemoptysis, following which he was admitted to the hospital. He made steady progress under treatment. The initial roentgenogram showed extensive tuberculous infiltration in both upper lobes. The three-month roentgenogram showed marked improvement.

Case 3. A 24-year-old man (motor mechanic) complained of "flu" which lasted for two weeks in November, 1954. One week later he suffered a relapse when a bad cough without sputum developed. He had pain across the shoulders, night sweats, and he lost 21 pounds in six weeks. On admission to the hospital in January, 1955, he appeared pale and ill. He made excellent progress on treatment and was discharged for family reasons after three months. He continued treatment at home. The initial roentgenogram showed extensive tuberculous infiltration of the right upper lobe and a 2 cm. cavity at the anterior end of the first rib. After two months of treatment the chest film had much improved and no cavity was visible. This improvement was maintained at three months.

Case 4. A 20-year-old man (clerk) had a hard dry cough for two months before admission to the hospital in December, 1954. On treatment he improved rapidly, gaining markedly

in weight and exhibiting striae across his loins. The initial roentgenogram showed infiltration of the upper third of the left lung and cavity (4.5 × 3.5 cm.) and also some infiltration of the right upper lobe. At three months no cavity could be recognized and the disease was much reduced in both apices.

Case 5. A 13½-year-old schoolboy developed pneumonia in December, 1954, which did not respond to routine treatment. He was admitted to the hospital in January, 1955, with a soft cough, which was worse in the morning. He had very little sputum. He had lost 7 pounds in weight and looked ill. He made satisfactory progress on treatment. His initial roentgenogram showed extensive infiltration in the left upper lobe and a 3 cm. cavity at the apex. There appeared to be a cavity in the right upper zone also. At the end of three months, cavitation was no longer recognizable and the infiltration was much reduced in extent.

Case 6. A 21-year-old waitress had a hard cough, severe in the morning, for three months before admission to the hospital. Her general condition was good and remained so during treatment. There were no weight changes before or during treatment. Her initial roentgenogram showed a rather fibrotic type of disease in both upper zones with multiple small cavities on the left side. At the end of three months she returned home, her roentgenogram showing some improvement and the presence of cavities doubtful.

Case 7. A 27-year-old woman (shop assistant) had had sanatorium treatment for pleurisy and pulmonary tuberculosis in 1942. An artificial pneumothorax was continued from 1943 until 1949. Thickening of the pleura resulted in an incarcerated lung and displacement of the mediastinum to the left. She was well from 1949 up to January, 1955, when she developed a cough. Roentgenograms, taken before the start of hinconstarch treatment, showed a thickened pleura over the left apex with an apparent atelectatic upper lobe containing several cavities. At the end of three months there was some, but not very marked, clearing. Thoracoplasty will be performed.

Case 8. A 40-year-old man (van driver) developed right pleural pain and night sweats at the end of December, 1954. He continued to work for some time but felt tired. He had occasional hard cough with scanty sputum. He has made steady progress under treatment. The initial roentgenogram showed infiltration of the right upper lobe with cavities (3 × 2.5 cm. and 1.5 × 1.5 cm.), confirmed by tomograms, at the anterior end of the first rib. There was also minimal disease in the left infraclavicular region. After three months there was considerable improvement in the roentgenographic appearance and tomograms showed no cavities.

Case 9. A 16-year-old girl (shop assistant) developed persistent cough following a cold in July, 1954. She continued to work until March, 1955, when amenorrhea caused her to consult her physician. She was admitted to the hospital in April, 1955. Clinically she did not look very ill although her evening temperature was always at least 102°F. The initial roentgenogram showed extensive pneumonic disease in the right lung, involving the upper lobe and with spread through the mid zone. Under treatment her pyrexia continued for five weeks. Her temperature then fell to normal and has remained so. Her cough has completely disappeared. The roentgenogram at three months showed atelectasis of the right upper lobe and bronchopneumonic shadows throughout the middle lobe.

Case 10. A 37-year-old man (laborer) had a left thoracoplasty without chemotherapy in 1948–1949. He resumed work as a laborer in 1953. In January, 1955, he was admitted to the hospital with tuberculosis of the right lung. His general condition was poor but improved considerably during treatment. The initial roentgenogram showed an apparently effective left thoracoplasty and acute bronchopneumonic disease with a cavity (1 cm.) in the right

lung. After three months, a roentgenogram showed slight to moderate improvement in the pneumonic disease and no cavity.

Case 11. A 53-year-old man (cattle drover) was admitted to the hospital with a six-week history of cough with sputum and pain in the left chest. The initial roentgenogram showed infiltration of the left apex. After three months the infiltration had cleared.

Case 12. A 36-year-old man (machinist) was admitted to the hospital with a four-month history of cough with sputum. The initial roentgenogram showed a cavity (5 cm.) with scattered soft infiltration throughout the upper lobe. After three months the cavity had reduced (3 cm.) while the infiltration remained unchanged.

Bacteriologic Findings

Specimens of sputum obtained fortnightly from each patient gave consistently positive results on culture for tubercle bacilli, both before admission to the investigation and during its early stages (table 4). Negative cultures were obtained in 10 of the 12 cases at the end of the twelfth week. Tubercle bacilli were cultured from *Patient No. 5* after fourteen weeks of therapy but three cultures, at fortnightly intervals since then, have been negative. The mean time required for the reversal of infectiousness was nine and two-tenth weeks. The progressive nature of the fall in the number of culturable tubercle bacilli excreted may be seen in table 4.

TABLE 4

RESULTS OF CULTURES FOR TUBERCLE BACILLI

Patient Number	Week of Sputum Specimen							
	0	2	4	6	8	10	12	14
1	+++	+++	++	++	++	++a	+b	+c
2	++	++	+	2	—	—	—	—
3	+++	++	+++	+	5	3	—	—
4	+++	—	+++	—	—	—	—	—
5	+++	+++	+++	+	1	—	—	5
6	++	—	—	—	—	—	—	—
7	+++	0	+	0	+	—	—	—
8	++	+	++	+	8	11	—	—
9	++	++	+	+	7	5	—	—
10	++	++	++	+	—	0	—	—
11	+	+	—	—	0	0	—	—
12	+++	+++	0	0	+d	+e	+f	0

0 = Examination not done
+++ = Heavy growth (uncountable colonies per control tube of medium)
++ = 40 to 200 colonies per control tube
+ = Less than 40 colonies per control tube (where less than 15 per tube, actual number given)
a = Approximately 1 per cent resistant to 0.2 γ of isoniazid per ml.
b = Susceptible to 0.2 γ of isoniazid per ml.
c = All resistant to 0.2 γ of isoniazid per ml.
d and e = Resistant to 5 γ of isoniazid per ml.
f = Resistant to 25 γ of isoniazid per ml.

Strains of tubercle bacilli from all patients were susceptible to isoniazid concentrations of 0.2 γ per ml. at the commencement of the investigation. Although it was not a condition of acceptance for the trial, these strains were also susceptible to 1 γ of streptomycin per ml. and to 1 γ of PAS per ml. In *Patient No. 1*, at the end of the tenth week of therapy, a single colony of *M. tuberculosis* was obtained on the isoniazid (0.2 γ per ml.) culture as compared with good growth on the control tubes, i.e., approximately 1 per cent resistant bacilli. A fortnight later the growth was drug-susceptible, but the next specimen gave equally good growth on the plain and 0.2 γ per ml. tubes. *Patient No. 12* discharged tubercle bacilli resistant to 5.0 γ of isoniazid per ml. at the end of the eighth and tenth weeks and bacilli resistant to 25 γ per ml. at the end of the twelfth week after the start of hinconstarch therapy.

Drug Toxicity

Patient No. 10 complained of occasional gastrointestinal discomfort. However this patient has a small duodenal ulcer of long standing, making it difficult to assess the role, if any, of the hinconstarch in these upsets. It was not necessary to interrupt his therapy at any time. *Patient No. 12* complained of severe epigastric discomfort on the fifty-fourth day of treatment. Hinconstarch was stopped for one day and then resumed. The discomfort did not recur. Apart from these doubtful instances, there was no other subjective evidence of drug toxicity in these 2 cases. *Patient No. 4* developed an urticarial rash on the second day of hinconstarch therapy but this disappeared after two days although treatment was continued. No subjective toxic effects of any kind were noted by the other patients.

In 3 of the 12 cases, indirect Van den Bergh tests with values outside the normal range (*Patients Nos. 4, 11,* and *12*) were observed (table 5). *Patients Nos.*

TABLE 5

SERUM BILIRUBIN (VAN DEN BERGH) AND HEMOGLOBIN ESTIMATIONS

Patient Number	Indirect Van den Bergh (Units) 3 Months	Hemoglobin (gm./100 ml.)	
		Start	3 Months
1	0	8.5	12.0
2	1.0	15.0	15.5
3	0.5	13.0	14.0
4	3.0	14.5	15.0
5	1.5	11.5	13.0
6	1.0	12.5	12.0
7	0.5	12.0	12.5
8	0	14.5	14.5
9	0	9.5	13.0
10	0.2	*	12.5
11	4.0	*	*
12	2.2	*	11.0

* Not available

TABLE 6

AMOUNT OF HINCONSTARCH PER PATIENT (IN GRAMS)

Patient Number	1	2	3	4	5	6	7	8	9	10	11	12
Starting daily dose	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.9	0.3	0.9	0.9
Final daily dose	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.6	1.6	1.2	1.2	1.2
Total for 3 months	84.8	71.7	71.0	72.2	80.3	70.6	75.0	92.8	129.2	88.1	88.5	95.5

11 and *12* had bilirubin values of 4.0 and 2.2 units as compared with 7.6 and 6.6 units, respectively, before the start of treatment. No patient developed anemia and no abnormality was noted in the other hematologic studies.

In no case was there clinical evidence of jaundice, and the direct Van den Bergh test was always negative. Thymol turbidity, serum protein, and alkaline phosphatase estimations gave results within normal limits throughout.

DISCUSSION

Hinconstarch is a chemical combination of *p*-aminobenzalthiosemicarbazone, isoniazid, and periodate-oxidized starch and cannot be regarded as a mixture of isoniazid and a thiosemicarbazone, nor even as a mixture of derivatives of these compounds. Evidence of this is that, while thiosemicarbazide itself ($NH_2 \cdot NH \cdot CS \cdot NH_2$) exhibits no antituberculous activity in mice, the polymer thiostarch, formed when thiosemicarbazide is condensed with oxidized starch, has such activity (4). The metabolism of hinconstarch in humans is being studied.

In a variety of clinical types of pulmonary tuberculosis, the clinical, roentgenographic, and bacteriologic changes, observed over a period of three months, would appear to be at least as good as those obtained with other regimens. The roentgenographic changes were noteworthy, improvement being observed in all cases. Of the 9 patients with cavities, the cavities were no longer present in 5 and possibly in 6. In one case (*Patient No. 11*), the abnormalities had completely cleared roentgenographically.

As judged by the results of sputum culture for tubercle bacilli, reversal of infectiousness occurred in 10 of the 12 patients. The emergence of isoniazid-resistant bacilli in *Patient No. 12* and of bacilli of decreased susceptibility in *Patient No. 1* was not altogether unexpected. For, in the early stages of the investigation, when the extent of the thiosemicarbazone detoxication in human patients was unknown, it was necessary to start with what are now known to have been inadequate doses and to increase these very gradually. These suboptimal doses, especially in patients with cavities, may have favored the emergence of resistant strains. Now that an effective dose has been established, however, one may expect that isoniazid resistance will not be an early or prominent feature of future cases. Slow emergence of resistance is to be expected, judging by the activity of hinconstarch in isoniazid-resistant infection of mice (4).

Boehm and Brecke (5), in a series of 245 cases treated with *p*-acetylaminobenzalthiosemicarbazone (amithiozone), noted toxic manifestations in 62 per cent of patients. In 21 per cent of all the patients, the drug toxicity was severe enough

to require the cessation of treatment. Gastrointestinal toxicity was marked, anorexia being noted in 44 per cent and vomiting in 18 per cent of the cases. As may be seen from the appetites recorded in table 1, anorexia was not a feature of hinconstarch therapy nor was vomiting observed. With amithiozone, hemolytic crises were seen mainly in patients who received 0.5 gm. daily—a dose now recognized as toxic—but with doses of 0.2 or less they were a relatively rare phenomenon (6). The evidence of small amounts of hemolysis present in 3 of the hinconstarch cases has therefore not been alarming.

The nonspecific decrease in the erythrocyte sedimentation rate, which usually occurs within a few days with amithiozone, was not observed with hinconstarch.

The absence of toxic reactions, the therapeutic efficiency, particularly in cavernous disease, and the ease of administration of a tasteless drug suggests strongly that hinconstarch should have a definite place in the chemotherapy of tuberculosis. Further clinical investigation should be directed to establishing the effectiveness of hinconstarch therapy as compared with the other chemotherapeutic regimens now in use for the treatment of pulmonary tuberculosis.

SUMMARY

Hinconstarch, a polymeric molecule derived from periodate-oxidized potato starch by condensation with equimolar proportions of isoniazid and *p*-aminobenzalthiosemicarbazone, has been investigated in 12 cases of pulmonary tuberculosis over a period of three months. The drug was given orally in daily doses ranging from 1.2 to 1.6 gm. The therapeutic effect of the drug was at least comparable with that of the best chemotherapeutic agents in present use. There were no significant toxic manifestations.

SUMARIO

El Hinconstarch en el Tratamiento de la Tuberculosis Pulmonar: Informe sobre Una Investigación Exploradora

El hinconstarch, molécula polimérica derivada del almidón de patata peryodato-oxidato por condensación con proporciones equimolares de isoniacida y *p*-aminobenzaltiosemicarbazona, fué investigado en 12 casos de tuberculosis pulmonar durante un período de tres meses. La droga fué administrada oralmente a dosis diarias que variaban de 1.2 a 1.6 gms. El efecto terapéutico fué a lo menos comparable al de los mejores agentes quimioterapéuticos en uso actualmente. No hubo mayores manifestaciones tóxicas.

RESUME

Hinconstarch dans le traitement de la tuberculose pulmonaire: Rapport sur une investigation "pilote"

L'hinconstarch est une molécule polymère dérivée de fécule de pomme de terre oxydée par l'acide périodique par condensation avec une proportion équimolaire d'isoniazide et de *p*-aminobenzolthiosemicarbazone. L'hinconstarch a été étudié pendant une période de trois mois dans 12 cas de tuberculose pulmonaire. Ce composé était donné par voie buccale. Les doses variaient entre 1, 2 g. et 1, 6 g. par jour. L'action thérapeutique de la drogue se comparait favorablement avec les meilleurs agents chimiothérapeutiques actuellement en usage. Il n'y a pas eu de réactions de toxicité appréciable.

Acknowledgments

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LYMPH NODE TUBERCULOSIS IN NECK, AXILLA, AND GROIN[1, 2]

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INTRODUCTION

Lymph node tuberculosis in neck, axilla, and groin has been discussed in the literature since the fifth century but during the past thirty-five years it has been generally considered a closed subject. The use of chemotherapy has again aroused interest in the condition. Gale (1) has reported on 210 cases in the Toronto Hospital for Tuberculosis during a period of twenty years, and Trautmann (2) has reported on 186 cases in Germany. Furthermore, the Committee on Therapy of the American Trudeau Society has urged that a study be made of the condition (3). Thus, it seems in order for the writers to discuss their experience in this field, since surgery is employed often on this service; hence, a considerable quantity of pathologic material is available for study.

MATERIAL AND METHODS

The present report deals with 66 patients with tuberculous lymphadenitis treated since the advent of tuberculosis chemotherapy, most of them since 1950. A few of them were private patients but all of the remainder came from the Chest Service of Bellevue Hospital, New York; hence, the patients were mostly adults. Medical treatment alone was employed in 12 cases and surgery was used in addition to medical treatment in 54. No operative cases of tuberculous lymphadenitis have been omitted.

Pathologic study was made of the specimen in every instance and, in many, bacteriologic study as well. It is therefore possible to observe the pathologic condition in connection with the clinical appearance and the chemotherapy. Some follow-up information was obtained in approximately 90 per cent of the surgical cases, but this was not as complete as it should have been. Considering the vagrant type of patient in the study, however, it was better than anticipated.

A larger number of patients received medical treatment alone but, because many abandoned treatment early in the study and could not be traced, only 12 of these are included.

OBSERVATIONS

Of the 66 cases, the lymph nodes of the neck were involved in 65. In addition, the axillary nodes were also diseased in 8 and the inguinal nodes in one patient. In one case, the only demonstrable lesion was in the inguinal nodes, a rather unusual occurrence.

Infection in a lymph node implies a primary infection elsewhere, but is frequently impossible to demonstrate. In table 1 the location of the tuberculosis is shown and the cases treated by surgery are listed separately from those in which the only treatment was medical. It may be seen that in nearly half of the cases no active lesion could be found other than that in the nodes. An active

[1] From the Chest Service of Bellevue Hospital, New York, New York.

[2] Presented before the Medical Session, as part of *Section 5A*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 24, 1955.

TABLE 1

SITE OF LESIONS

	Surgical	Medical
Nodes only	30	6
Superficial lesion	2	0
Pulmonary	20	5
Active	14	4
Inactive	6	1
Disseminated	2	1

superficial lesion in the area drained by the diseased nodes could be demonstrated in only 2 cases. Evidence of a pulmonary lesion was found in 25 patients and in 18 of these the disease was active. In 7, the pulmonary lesion had previously been treated and was presumably inactive. In 3 instances the disease was disseminated and present in tissues other than the lungs and lymph nodes. Thus, demonstrable, widespread infection was not the rule.

Study of the pathologic condition of the nodes with respect to the clinical manifestations indicates that there is a high degree of correlation. At the start of the lymph node disease the pathologic reaction is that of acute inflammation corresponding to the acute phase of a pulmonary lesion. Tubercles and caseation necrosis are absent. Clinically, this is manifested by the rather abrupt appearance of a swelling so tender that it suggests acute suppurative lymphadenitis. The involved nodes are not matted together. A febrile reaction is usually present.

The process can be arrested at this point, but the caseous material frequently becomes liquefied in time. The cold abscess thus formed gradually penetrates the perinodal fibrosis into the surrounding tissue and eventually perforates the skin, forming a sinus tract. At the bottom of the tract there is usually a group of caseous nodes. Clinically, the pre-existing swelling enlarges, becomes tender, and later fluctuates and discharges. If all of the caseous material has become liquefied, the discharge gradually diminishes and the wound heals. Unfortunately this is not the rule because there is usually enough caseous tissue to keep the sinus from healing permanently.

The final stage is the deposition of calcium in the diseased tissue which acts as a foreign body.

TABLE 2

NO DISTANT LESIONS

X-Ray Treatment Was Used Unsuccessfully in 6 Cases

Preoperative Chemotherapy	Patients	Recurrence		
		None	Early	Late
None	3	2	1	0
Less than 3 weeks	10	9	1	0
3 weeks plus	10	9	0	1
Multiple	9	3	1	5

Prior to the use of chemotherapy, the medical treatment of tuberculous lymphadenitis was not specific and the pathologic examination was simply a diagnostic procedure. Chemotherapy, however, is a more or less definitive treatment, and the pathologic study of the tissue is important as a means of appraising the value of this therapy. It is used routinely and it has been found that chemotherapy seems to act on the infection in the lymph nodes in much the same way that it does in the lungs. Streptomycin or isoniazid with PAS have been used and, occasionally, all three have been administered together. Chemotherapy is most effective in the exudative phase of the disease. It cannot remove caseous material, and the organism will become resistant to it in time. The lymph node response can best be illustrated by citing clinical cases.

Case Reports

A 16-year-old male entered the hospital with a tender swelling in his groin which had appeared quite abruptly. He had a fever as high as 102°F. at times. He was treated for an acute pyogenic lymphadenitis for three weeks with no improvement. It was then decided to use streptomycin-PAS, although a careful study, including a roentgenogram of his lungs, showed nothing suggestive of tuberculosis. After eighteen days of chemotherapy, there was no apparent change in the condition except a reduction in the fever. Surgical excision was decided upon but it was not possible to schedule the operation for several days. During this time the swelling regressed markedly; nevertheless, the operation was performed.

The pathologic examination showed a lymph node with definite inflammatory reaction and points of acute necrosis, together with tubercles and giant cells but no caseation necrosis. Healing eventually occurred but was complicated by a serous discharge from the wound. From the clinical response to the drug and from the pathologic appearance of the specimen, it would seem that healing had started and would have taken place on chemotherapy alone.

The second case was that of a 36-year-old male who entered the hospital with pneumonia. While still under treatment, a group of supraclavicular lymph nodes, which had been enlarged for years, increased in size and remained enlarged after the pneumonia had resolved. Treatment with streptomycin-PAS was started and the nodes receded somewhat but were still larger than they were on admission. After three weeks the recession ceased and for the next five weeks there was no change although chemotherapy was continued. The nodes were then excised.

On pathologic examination the lymphoid tissue was found to be almost completely replaced by caseation necrosis. There was no inflammatory reaction. Apparently the maximum effect of the drugs had been obtained, but the caseous material remained. Recovery was prompt and complete.

The third case involved a 26-year-old female who had previously been successfully treated for renal and pulmonary tuberculosis. While in the hospital at that time, a group of tuberculous nodes were removed from the right supraclavicular region. She was discharged from the hospital and returned to work, still continuing the chemotherapy.

One year later, while the patient was still on chemotherapy, a tender swelling appeared just below the angle of her right jaw. This increased in size for a time and then suddenly disappeared. Coincident with the disappearance, a fluctuant swelling appeared in the scar of the previous operation and drained spontaneously. The mass below the angle of the jaw could barely be palpated but incision was made over it and a mass of caseous nodes was removed from behind the sternomastoid muscle. A sinus tract went from these nodes to the discharging sinus in the old scar. This was also removed. The operative wounds healed

promptly and have remained healed. Chemotherapy had been employed continuously for more than two years; it had controlled the pulmonary and kidney lesions but not the lesion in the caseous nodes.

A fourth case was that of a 35-year-old male who entered the hospital with a large cold abscess in the left side of his neck. Chemotherapy was instituted and the abscess was drained. The wound was irrigated daily with streptokinase-streptodornase solution; it eventually healed and the patient was discharged.

About two months later, while still on chemotherapy, the patient returned to the hospital with another cold abscess in the same area. This was evacuated and the underlying caseous nodes were removed. Culture of the purulent material was negative for tubercle bacilli. The wound healed promptly and has remained healed. Chemotherapy could not prevent the formation of a cold abscess in the presence of caseation necrosis, even though the organisms were apparently inhibited.

The surgery which was used in these operations is a definitive treatment and implies the *removal of all of the diseased nodes through incisions which heal with minimal scarring and with the preservation of all of the important anatomical structures.*

The neck operation is the most important and the most common. The incisions are shown in figure 1 and follow the natural creases of the neck. The operation is radical and time-consuming but differs materially from the radical neck dissection for malignancy. When dealing with malignancy, important structures are sacrificed to eliminate all possible disease-bearing tissue. When dealing with tubercu-

FIG. 1. Sketch showing that incisions follow creases in the neck. It is seldom necessary to use all in one operation.

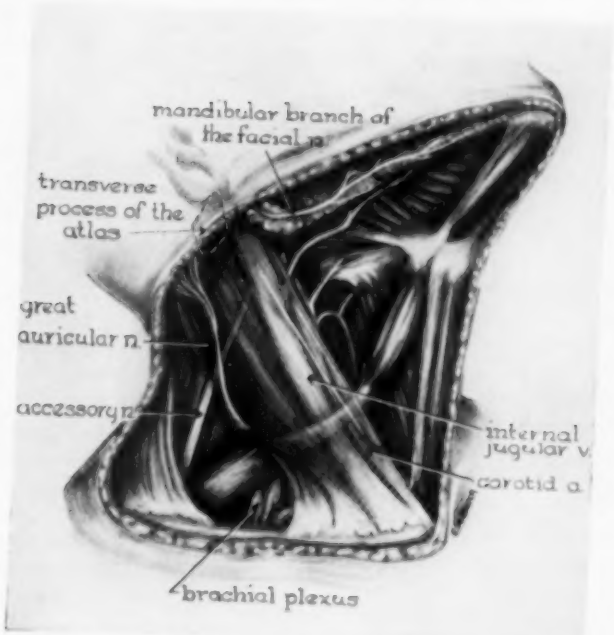

FIG. 2. Anatomical sketch of the neck. Structures to be preserved are sternomastoid muscle, accessory nerve, mandibular branch of facial nerve, brachial plexus, jugular vein, and common carotid artery.

losis, such thoroughness is unnecessary because, if the remaining nodes become diseased, they can be removed at another operation—something which would imply failure with malignancy.

The technique has previously been described (4) and in figure 2 the important structures to be preserved are shown. With due care this can be accomplished although occasionally the mandibular branch of the facial nerve may be injured, often only temporarily.

A small cold abscess situated in a mass of nodes is treated preferably by excision of the abscess and the underlying nodes. When the abscess is large, drainage is done as a preliminary measure through a carefully placed incision large enough to permit subsequent instillation of streptokinase-streptodornase solution to dissolve the accessible caseous material.

If a biopsy is made, all of the nodes in the field should be removed. To take less invites the formation of a cold abscess in the scar.

RESULTS

For presentation of the results of surgery the cases are listed in three main groups: (*1*) Those in which the clinical disease was confined to the lymph nodes plus the 2 cases in which the involved nodes drained a superficial tuberculous

infection; (*2*) those in which clinical disease was also present in the lungs; and (*3*) those in which clinical disease was present in many organs. The patients not treated by operation are discussed separately.

At the time of writing this paper, all surgically treated lesions had been healed for more than six months but this obviously does not mean that there will never be a recurrence of tuberculous lymphadenitis in these patients. Recurrence as mentioned in the tables implies that another operation was performed. Drug therapy refers to preoperative drug therapy. All patients had drug therapy for a time after operation.

Of the 54 surgically treated cases, the clinical disease was confined to the lymph nodes in 32, except as mentioned directly above. In 13 cases the disease was so old and so well localized that preliminary chemotherapy was limited. The infected nodes were removed at once when the patient presented with fluctuation in the swelling. This was to forestall the secondary infection which would follow rupture of the abscess. Early recurrence probably indicated that some of the diseased nodes had been overlooked at operation. Late recurrence probably indicated fresh disease or renewed activity in an old, small, previously quiescent lesion.

The patients who had multiple forms of preoperative therapy presented a special problem. All were of long standing and had been treated by many diverse methods. One patient, a woman of thirty-six, had had lymph node infection for twenty-nine years. There were draining sinuses in both sides of the neck, in both axillae, and both groins. After numerous operations the disease seemed to be eradicated and more than a year has elapsed without recurrence. The other patients had similar but less extensive disease. As would be expected, there was more recurrence in this type than in any other.

In the next group of 14 cases there was active infection in the lungs as well as in the lymph nodes (table 3). In 11 of these patients the sputum was positive for *M. tuberculosis* and all were in the hospital because of the pulmonary lesion. Since the pulmonary lesion was more important, the treatment was directed toward this. Bed rest and chemotherapy were employed extensively and no special attention was directed to the nodes until the pulmonary lesion had become stable. Before chemotherapy, operation would not have been undertaken on these nodes but, with the pulmonary lesion controlled by the drugs, the diseased nodes could be removed surgically with safety.

TABLE 3

ACTIVE PULMONARY LESIONS

All Had Prolonged Chemotherapy Before and After Node Operation

Node Recurrence			Lung		
None	Early	Late	Inactive	Active	Lost
12	1	1	11	2*	1

* Still under treatment.

TABLE 4

HEALED PULMONARY LESIONS

Preoperative Chemotherapy		Patients	Recurrence	
Lung	Nodes		Nodes	Lung
1	None	1*	0	1
	Less than 3 weeks	3	0	
	3 weeks plus	2	1 (late)	

* Patient developed lymph node lesion sixteen months after pulmonary lesions had been treated chemotherapeutically.

In 6 cases, lymph nodes became infected months or years after a previously treated pulmonary lesion had been considered inactive (table 4). In 5 of the 6 cases chemotherapy was not available for the original treatment, and in only 2 cases was chemotherapy used for more than three weeks before operation. The only recurrence was in a patient with more than three weeks' preoperative treatment. One patient had a fresh pulmonary lesion sixteen months after successful lymphadenectomy for caseous nodes with cold abscess.

Medical treatment alone was given in 12 cases. These cases are presented in table 5. In half of the patients there was an associated pulmonary lesion; in the others the disease was limited to the nodes. In half, the disease of the nodes was not very extensive. All of the rest were placed on bed rest which varied from five weeks to six years. All received chemotherapy, which comprised streptomycin-PAS in 11 cases plus isoniazid in 2. Isoniazid-PAS therapy was used without streptomycin in one case.

The results in this group are only fair. The disease in one patient is unchanged. She was a 72-year-old woman who stated that she had been afflicted with scrofula since childhood. She refused chemotherapy and left the hospital against medical advice after seventy days in bed. The other patients showed considerable improvement, and in 7 no nodes are palpable. The course of therapy was much longer than in the patients treated surgically and there is always the possibility that the tuberculous process in the nodes will flare up again.

TABLE 5

MEDICAL TREATMENT ONLY

	Patients	Size of Nodes			Bed Rest	Chemotherapy		
		+	++	+++		Streptomycin	PAS	Isoniazid
Nodes only	6	3	1	2	5 weeks to 18 months	5*	5	2
Pulmonary	6	3	0	3	2 months to 6 years	6	6	1

* One patient refused chemotherapy.
Streptomycin dosage varied from 10 gm. to 108 gm.
PAS dosage varied from 480 gm. to 6,475 gm.
Isoniazid dosage varied from 27 gm. to 63 gm.

It is unjustified to draw conclusions from this group, but it represents all of the patients who were willing to go through with the lengthy course of treatment. Many others started treatment but abandoned it before it was completed.

DISCUSSION

From the foregoing the writers are convinced that there is a correlation between the clinical appearance and the pathologic condition with respect to lymph node infection. The treatment must be predicated upon the pathologic state. In the acute phase, bed rest and other general supportive measures are indicated just as they are in any acute disease. In addition, chemotherapy seems to be most effective at this time. In the presence of caseation necrosis or cold abscess, the damage has already been done and little can be expected from such measures. Surgical removal is necessary to eradicate the disease. However, when most patients with tuberculous lymphadenitis present themselves for treatment they have a combination of the exudative type, caseation necrosis, and often cold abscess, so that the optimal treatment is not readily apparent. Moreover, an active lesion in the lungs or elsewhere may be present to further complicate the situation.

It is axiomatic that the treatment should be directed to the most important lesion first and, when this is under control, the other lesions can be dealt with. Fortunately, the general supportive measures and the chemotherapy apply alike to all forms of tuberculosis so that concentration on one type of lesion does not mean that the others are being neglected. It should be remembered that the treatment should be changed to meet the changing pathology. Thus, bed rest, sanatorium care, and general supportive measures may well be supplemented with other more definitive treatment when the acute phase has passed. It should also be remembered that surgery may be hazardous in the acute phase of tuberculosis and is most effective in the chronic and controlled lesions, and that the microorganisms become drug-resistant in time.

The writer's plan of treatment is based on a consideration of these factors. The acute phase of the disease is treated by bed rest, general supportive measures, and chemotherapy until the lesion has become stationary. Any enlarged nodes which remain are then removed surgically. If the disease is chronic when first seen, chemotherapy is used for approximately three weeks or as much longer as the nodes continue to shrink, and is then followed by surgical removal of any remaining nodes. One exception to this rule is the presence of fluctuation in a mass of nodes. In such a case, operation is performed at once to forestall the spontaneous rupture of the cold abscess with the consequent secondary infection in the wound. When an active pulmonary lesion is present, the treatment is directed to this first and, when this lesion is controlled, the lymph nodes are removed if any are palpable. When surgery for the pulmonary lesion is contemplated, the lymph node operation is performed first. Cold abscess is treated as described above. Chemotherapy is continued after operation as long as indicated, usually until the wound has healed.

X-ray treatment, once quite popular, has largely been replaced by chemo-

therapy. If sinuses persist after the removal of all of the caseous material possible, X-ray treatment is used, especially when the organism is drug-resistant. Irradiation is nonspecific therapy but may be quite effective under these conditions.

Surgery is important in our treatment of tuberculous lymphadenitis in contradistinction to what seems to be the general practice elsewhere. It is hard to understand why surgery has come into disfavor for lymph node tuberculosis when its use in the pulmonary form of the disease has become so popular. This is especially true since the surgical treatment was so successful shortly after the turn of the present century (5), long before antituberculous chemotherapy had been discovered and at a time when even the roentgenographic diagnosis of pulmonary tuberculosis was a rarity.

SUMMARY

Tuberculosis of the lymph nodes of neck, axilla, and groin has been observed in 66 patients treated since the advent of antituberculous chemotherapy. More than half of the patients had no demonstrable lesions elsewhere and only 2 had lymph node disease in the area draining a superficial infection. Pulmonary lesions, active at the time or which had previously had prolonged and successful treatment, were present in 25 instances.

Adequate bed rest is a necessary adjunct in the acute cases and in patients with disease in other organs. In the experience of the present writers it has not been successful in chronic lymph node disease and merely prolongs the course of therapy.

X-ray therapy has largely been replaced by chemotherapy, although there are still definite indications for its use.

Chemotherapy has made possible the resection of tuberculous nodes in the presence of tuberculosis elsewhere. It is invaluable in the acute cases and helpful in the chronic ones.

Adequate surgery at the proper time and in conjunction with other forms of treatment is still the most successful means of eradicating lymph node tuberculosis in accessible areas.

SUMARIO

Tuberculosis de los Ganglios Linfáticos del Cuello y de la Axila y la Ingle

Observóse tuberculosis de los ganglios linfáticos del cuello y de la axila y la ingle en 66 enfermos tratados desde el advenimiento de la quimioterapia antituberculosa. Más de la mitad de los sujetos no tenían lesiones observables en otras partes y solamente 2 tenían afección linfoganglionar en la zona que canalizara una infección superficial. En 25 casos, existían lesiones pulmonares, activas todavía o que habían recibido antes tratamiento prolongado y eficaz.

El descanso adecuando en cama es un coadyuvante necesario en los casos agudos y en los enfermos que tienen afectados otros órganos. En lo observado por el A., no surte efecto en la enfermedad crónica de los ganglios linfáticos y meramente prolonga la serie de terapéutica.

La roentgenoterapia ha sido suplantada en gran parte por la quimioterapia, aunque todavía existen indicaciones bien definidas para su empleo.

La quimioterapia ha hecho posible la resección de ganglios tuberculosos, aun existiendo tuberculosis en otro sitio. Es insuperable en los casos agudos y útil en los crónicos.

La cirugía adecuada en el momento apropiado y combinada con otras formas de tratamiento ofrece todavía el medio más adecuado para erradicar la afección de los ganglios linfáticos en los sitios accesibles.

RESUME

Tuberculose des ganglions lymphatiques cervicaux azillaires et inguinaux

La tuberculose ganglionaire des régions cervicale, axillaire et inguinale a été observée chez 66 malades traités depuis l'apparition de la chimiothérapie antituberculeuse. Dans plus de la moitié des cas il n'y avait pas de lésions apparentes ailleurs et 2 seulement présentaient des lésions ganglionnaires dans la zone de drainage d'une infection superficielle. Des lésions pulmonaires, en activité à ce moment ou qui avaient été antérieurement soumises à un traitement prolongé et satisfaisant, étaient présentes dans 25 cas.

Le repos adéquat au lit est un adjuvant nécessaire dans les cas aigus lorsque l'affection s'étend à d'autres organes. Selon l'expérience acquise par les auteurs, l'alitement a été sans succès dans l'adénopathie chronique, il prolonge simplement la durée du traitement.

La radiothérapie a été largement remplacée par la chimiothérapie, bien que son emploi ait encore des indications bien définies.

La chimiothérapie a permis la résection des ganglions tuberculeux en présence de lésions tuberculeuses en d'autres points. La chimiothérapie est irremplacable dans les cas aigus et elle est utile dans les cas chroniques.

L'intervention chirurgicale adéquate, au moment opportun, associée aux autres formes de traitement constitue encore le moyen le plus satisfaisant pour l'éradication des adénopathies dans les régions accessibles.

Acknowledgment

The writers express their gratitude to Dr. Marvin Kuschner for his valuable assistance with the interpretation of the pathology in the present report.

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CALCIFICATION OF REGIONAL LYMPH NODES FOLLOWING BCG VACCINATION[1]

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(Received for publication July 11, 1955)

INTRODUCTION

A primary tuberculous infection is characterized by the formation of a nodule at the site of localization of the tubercle bacillus which is associated with involvement of the regional lymph nodes. The involved nodes undergo swelling, caseation necrosis, encapsulation by connective tissue, and inspissation of the necrotic material. In a high percentage of cases the process is followed by calcification of the necrotic area. Many factors, such as the dose and virulence of the organism, the route of infection, the anatomic relationship of the regional nodes, the race, age, and degree of natural resistance of the individual, influence the rapidity and extent of involvement and the nature of the pathologic changes in the draining lymph nodes.

That the character of the inflammatory reaction is modified by the avirulence or virulence of the tubercle bacillus has been shown by Medlar and Sasano (1) as well as by Smithburn (2). These investigators found that pulmonary lesions induced in rabbits by avirulent or attenuated strains of tubercle bacilli tend to be localized, to develop slowly, to consist essentially of monocytes, and to be surrounded by lymphocytes and connective tissue. On the other hand, virulent cultures of tubercle bacilli induce an acute inflammatory reaction, with abscess formation, numerous polymorphonuclear cells, and a tendency to invasiveness.

In an attempt to evaluate objectively the influence of race and age in tuberculosis, Aronson and Sokoloff (3) compared the local reaction to the attenuated BCG culture in white and Negro infants and in adults who failed to react to tuberculin.

This study was carried out by injecting freshly prepared BCG vaccine into the skin over the region of the deltoid of white and Negro infants within twenty-four to forty-eight hours after birth and in adults of various ages who failed to react to tuberculin. The vaccine was prepared from BCG culture No. 793 originally obtained direct from the Pasteur Institute in Paris. At various intervals following vaccination, the infants were visited by a specially trained nurse who examined and described the local lesion at the site of injection and who palpated and examined the nodes in both axillas to determine whether they were enlarged or had suppurated. It was found that 22.6 per cent of 287 white infants and 17.5 per cent of 1,618 Negro infants showed enlargement of the axillary nodes draining the site of the BCG vaccination. Suppuration of these nodes was observed in 3.5 per cent of the white and in 5.8 per cent of the Negro infants. On the other hand, only 5 of the 6,084 adults who had received an intracutaneous injection of BCG vaccine complained of swelling of the regional axillary nodes and in no instance did the nodes suppurate.

[1] From the Henry Phipps Institute of the University of Pennsylvania, Department of Health, Philadelphia, and Jefferson Medical College, Philadelphia, Pennsylvania.

Since calcification frequently occurs in the tuberculous hilar nodes, especially in children (4), a study was undertaken to determine whether calcification of the nodes draining the site of BCG vaccination occurs and whether it is related to the swelling or suppuration of these nodes.

MATERIAL AND METHODS

Through the city chest clinics and the cooperation of the public health nurses, contact was established with the parents or guardians of the 4,513 infants who had received an intracutaneous injection of BCG vaccine shortly after birth. The parents or guardians were requested to bring the infant to a designated clinic for roentgenographic examination. As a result of this effort, 34 white and 471 Negro infants received a roentgenographic examination of the chest and axilla. The films were interpreted by one of the writers (SCS), who had reviewed the films of the BCG study in Indians (5), and shadows either single or multiple which had the density of bone were interpreted as calcium. The interval between vaccination and roentgenographic examination ranged from one to fifty-four months.

OBSERVATIONS

Among the 34 white and 471 Negro infants who were examined roentgenographically, evidence of visible calcification of the regional axillary nodes draining the site of BCG vaccination was found in 7 (20.6 per cent) of the white infants and in 42 (8.8 per cent) of the Negro infants. Of the 15 white males and the 19 white females, 3 (20.0 per cent) of the former and 4 (21.0 per cent) of the latter showed calcification of the axillary nodes. Among the Negro children, 34 (13.6 per cent) of the 247 males and 18 (8.0 per cent) of the 224 females showed calcification of the regional axillary nodes. The number of white children included in this study is too small to be statistically significant. Nevertheless, it is noteworthy that a significantly higher percentage of white than Negro infants showed healed calcified axillary nodes. These observations are in accord with those noted by Brailey (6) who found that 30.0 per cent of white children had unhealed intrathoracic tuberculous lesions while 55.0 per cent of Negro children of the same age group showed such unhealed lesions.

The time factor in the roentgenographic appearance of calcification following known tuberculous infection has been dealt with by Sweany (7). Brailey (6) noted calcification of the hilar nodes in a ten-month-old infant who had been exposed to tuberculosis in the first month of life and who became tuberculin-positive at six weeks of age. Further data regarding the interval between tuberculous infection and the appearance of calcification were derived from the records of the tragic accident which occurred in Lübeck, Germany, in 1930. Here, 251 infants received, *per os*, three doses of a vaccine prepared from a culture of a virulent human-type tubercle bacillus. Seventy-seven of the 251 infants died. Calcification of lymph nodes was observed as early as fifty-eight days after infection, and twenty to twenty-one months after infection calcification of nodes was noted regularly.

The vaccination of new-born infants with BCG vaccine offered an opportunity to determine the frequency and time of appearance of calcification of the regional axillary nodes draining the local ulcer induced by the BCG vaccine. An example

FIG. 1. (J. H.) Roentgenogram taken at three months, showing development of calcium in the left axillary nodes. Vaccination in November, 1950.

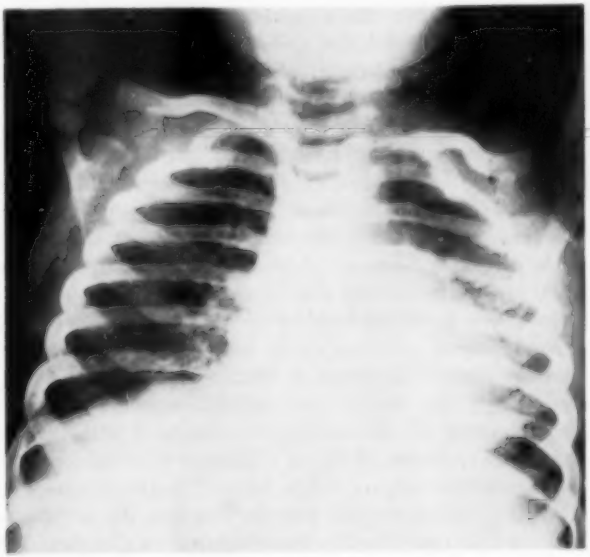

FIG. 2. Roentgenogram taken at seven months.

TABLE 1

CALCIFICATION OF AXILLARY NODES BY RACE, SEX, AND TIME OF OBSERVATION

Age in 6-Month Periods	White						Negro						Total		
	Males			Females			Males			Females					
	Number Examined	Calcified		Number Examined	Calcified		Number Examined	Calcified		Number Examined	Calcified		Number Examined	Calcified	
		Number	Per Cent		Number	Per Cent		Number	Per Cent		Number	Per Cent		Number	Per Cent
Under 6	0	—	—	0	—	—	16	1	6.3	11	0	—	27	1	3.7
7–12	2	1	50.0	1	—	—	23	3	13.0	19	2	10.5	45	6	13.0
13–18	2	—	—	7	2	28.6	59	5	8.5	39	3	7.7	107	10	9.3
19–24	1	—	—	2	—	—	42	11	26.1	47	4	8.5	92	15	16.3
25–30	4	—	—	4	1	25.0	50	6	12.0	49	4	8.2	107	11	10.4
31–36	4	2	50.0	4	—	—	24	6	25.0	29	1	3.5	61	9	14.8
37–42	1	—	—	1	1	100.0	26	2	7.7	21	2	9.5	49	5	10.2
43–48	0	—	—	0	—	—	5	0	—	5	1	20.0	10	1	10.0
49–54	1	—	—	0	—	—	2	0	—	4	1	25.0	7	1	14.3
Total	15	3	20.0	19	4	21.0	247	34	13.6	224	18	8.0	505	59	11.6

of the development of calcification of the regional axillary nodes is given in figures 1, 2, and 3. Unfortunately, in this series the precise time when calcification of the nodes occurred cannot be stated since roentgenographic examinations were not made at repeated stated intervals. The frequency and time of observation of calcification by race and sex are summarized in table 1.

It will be noted from table 1 that a higher percentage of white infants than of Negro infants showed healed calcified axillary nodes. Even though the number of white infants is not statistically significant in this study, it is noteworthy that the percentage with calcification among the white infants is the same for both sexes while, among the Negro children, a significantly higher percentage of males than of females shows calcification. Calcification was noted in a Negro infant as early as two months after vaccination. The percentage of infants who showed calcification of the axillary nodes rose sharply in the group vaccinated seven to twelve months previous to the roentgenographic examination, and approximately the same percentage showed calcified nodes in the older age groups. The relative constancy of the percentage who showed calcified lesions, beginning with those vaccinated seven to twelve months previously, suggests that calcification probably occurred in most instances within one year after vaccination.

Since calcium is usually deposited in chronically inflamed areas, in which necrotic material, especially tuberculous material, is not completely removed or absorbed, the occurrence of calcification was correlated with the post-vaccinal condition of the axillary nodes. Of the 34 white and 471 Negro infants who were examined roentgenographically, 4 white and 47 Negro infants had not been seen prior to their roentgenographic examination and the post-vaccinal condition of the nodes was not known. The relationship of calcification of the axillary nodes to the post-vaccinal appearance of the nodes in those infants who had been seen is presented in table 2.

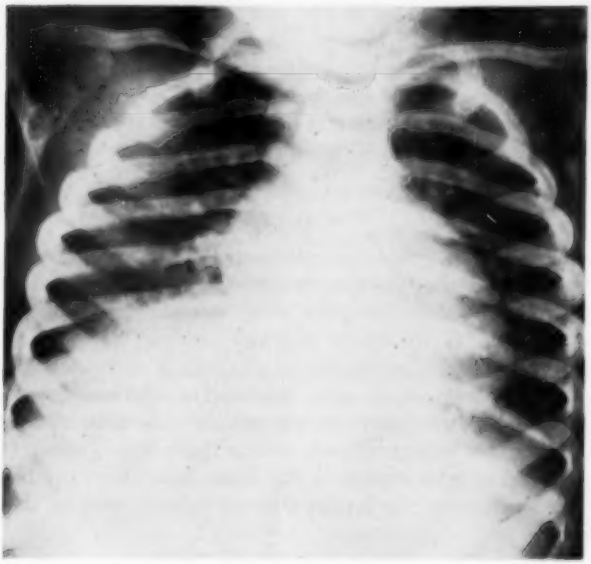

FIG. 3. Roentgenogram taken at eleven months.

Although the number of white infants studied are few, it is noteworthy that calcification occurred in a higher percentage of white than of Negro infants whose axillary nodes showed no visible or palpable enlargement. On the other hand, it is of interest that calcification did occur in a higher percentage of the Negro infants who showed either swelling or suppuration of the nodes than in those whose nodes were not involved.

The lack of correlation between the gross post-vaccinal appearance of the regional lymph nodes and calcification may be attributed, in the case of the enlarged nodes, to the fact that necrosis occurred in only a small percentage of such nodes. It is surprising that calcification did not occur more frequently in those

TABLE 2

CALCIFICATION OF AXILLARY NODES IN RELATION TO INITIAL CHANGES

Initial Condition of Axillary Nodes	White			Negro		
	Number Examined	Calcified		Number Examined	Calcified	
		Number	Per Cent		Number	Per Cent
Enlarged	4	1	25.0	43	14	32.5
Suppuration	0	0	—	20	5	25.0
Negative	26	5	19.2	361	32	8.8
Not seen	4	1	25.0	47	1	2.1
Total	34	7	20.6	471	52	11.0

which showed suppuration. This may be due to the fact that the necrotic material had been constantly eliminated from the node by drainage. It has been suggested that, when liquefaction takes place within the necrotic material before calcification sets in, there must first be an absorption of the fluid, then an inspissation of the necrotic contents, and then a deposition of calcium salts in the necrotic material. Thus, the time for calcification is prolonged because of this process.

COMMENT

The importance of the lymphatic system in the defensive mechanism of the organism is well recognized. The lymph nodes serve not only as a barrier to the passage of bacteria but also contribute to the defensive mechanism by the production of antibodies. In the course of many bacterial infections the bacteria localize in the lymph nodes, giving rise to an acute or chronic inflammatory reaction which may or may not go on to suppuration. The incomplete absorption of the necrotic material from tuberculous lymph nodes, associated with chronicity, favors the deposition of calcium in such dead or degenerating areas. It is possible that the more marked involvement of the nodes in infancy may be due to differences in the structure of the lymph nodes of infants, such as the absence of the germ center.

SUMMARY

Calcification of regional axillary nodes draining the site of BCG vaccination was demonstrated roentgenographically in 7 (20.6 per cent) of 34 white children and in 42 (8.8 per cent) of 471 Negro children. Calcification of the axillary nodes was observed as early as two months after vaccination. Calcification occurred somewhat less frequently among those whose lymph nodes had suppurated than among those whose nodes were swollen but did not suppurate, and less frequently when the nodes were not enlarged.

SUMARIO

La Calcificación de los Ganglios Linfáticos Regionales Consecutivamente a la Vacunación con BCG

En 7 (20.6 por ciento) de 34 niños de raza blanca y en 42 (8.8 por ciento) de 471 niños de raza negra, se descubrió radiográficamente calcificación de los ganglios axilares regionales que drenaban el sitio de la vacunación con BCG. Esa calcificación ya fué observada hasta a los dos meses de la vacunación. La calcificación ocurrió algo menos frecuentemente entre los niños cuyos ganglios habían supurado que entre aquéllos cuyos ganglios se habían hipertrofiado, pero no supurado, y menos frecuentemente cuando los ganglios no estaban hipertrofiados.

RESUME

Calcification des ganglions lymphatiques regionaux à la suite de la vaccination par le BCG

La calcification des ganglions axillaires régionaux en relation avec le siège de la vaccination par le BCG a été démontrée radiologiquement chez 7 (20,6 pour 100) des 34 enfants de race blanche et chez 42 (8,8 pour 100) des 471 enfants de race Noire. La calcification des ganglions axillaires a été observée dès deux mois après la vaccination. La calcification s'est

produite un peu moins fréquemment dans les cas où la suppuration ganglionnaire existait que parmi ceux où il y avait une hypertrophie des ganglions sans suppuration, et encore moins fréquemment lorsqu'il n'y avait pas d'hypertrophie ganglionnaire.

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PASSIVE TRANSFER OF TUBERCULIN HYPERSENSITIVITY IN GUINEA PIGS USING CELLS DISRUPTED BY SONIC VIBRATION[1,2]

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INTRODUCTION

Passive transfer of tuberculin hypersensitivity has been demonstrated in experimental animals through the use of peritoneal exudates (1–3), minced spleen (1, 3), and thoracic duct lymph (4). These studies suggested that successful passive transfer required intact, viable cells.

Recently Jeter and associates (5) were able to demonstrate passive transfer of delayed cutaneous hypersensitivity to 2,4-dinitrochlorobenzene in guinea pigs with extracts of sonic-disrupted leukocytes derived from peritoneal exudates of sensitized animals. Lawrence (6) succeeded in passively transferring tuberculin hypersensitivity in humans, employing extracts of leukocytes obtained from human plasma. The extracts were made by disruption of the cells with distilled water or by freezing and thawing. Ribonuclease and desoxyribonuclease did not destroy the active principle. More recently, Cole and Favour (7) showed that antibody to tuberculoprotein is contained exclusively in a new plasma fraction called fraction IV-10. This fraction is a part of Cohn's fraction IV (alpha globulin) and, to a lesser extent, fraction V (albumin). This new fraction (IV-10), obtained from highly sensitized guinea pigs, will passively transfer to normal guinea pigs a delayed skin sensitivity to tuberculin (PPD).

The writers have been able to show that extracts of sensitized cells from guinea pigs contain a factor which, when transferred to normal recipients, renders them sensitive to tuberculin (OT or PPD). This has been accomplished through the use of extracts of sonic-treated peritoneal cells prepared in a manner similar to the technique employed by Jeter and associates (5). The observations in the present study have also been extended to include extracts obtained from sonic-treated spleens of sensitized guinea pigs.

MATERIALS AND METHODS

In the first experiment, 40 male albino guinea pigs were made hypersensitive to tuberculin by the intramuscular injection of 0.3 mg. of heat-killed H37Rv in 1.0 ml. of paraffin oil. Thirty days later the animals were skin tested with 0.1 ml. of a 1:100 dilution of deglycerinated OT. The average reaction at twenty-four hours was 25 × 30 mm. At this point, peritoneal exudates were produced by the intraperitoneal injection of 30 ml. of sterile mineral oil. Forty-eight hours later the animals were killed and the cells of the exudate were pooled and washed twice with heparinized Ringer's solution. The packed cells (3 ml.) were then suspended in 6 ml. of heparinized Ringer's solution containing 10

[1] From the Tuberculosis Research Laboratory, Veterans Administration Hospital, Washington, D. C.

[2] Presented before the Medical Session, as part of *Section 4B*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 24, 1955.

per cent of normal guinea pig serum. Half of the cell suspension was injected intraperitoneally in 1.5 ml. amounts into each of 2 normal recipient guinea pigs. The other half was subjected to sonic vibration (9,000 cycles per second) in a Raytheon Magnetostriction Oscillator for fifteen minutes at 30°C. The resulting homogenate was centrifuged for fifteen minutes at 3,000 r.p.m. to separate the cellular debris from the clear supernatant fluid. The supernatant was then injected intraperitoneally in 1.5 ml. amounts into each of 2 normal guinea pigs.

Twenty-four and forty-eight hours after transfer, the recipient guinea pigs were skin tested with 0.1 ml. of a 1:4 dilution of deglycerinated OT. The reactions were measured and recorded after forty-eight hours.

In the second experiment, 30 male albino guinea pigs were sensitized by the intramuscular injection of 10 mg. of heat-killed H37Rv in 1.0 ml. of paraffin oil. Each animal was given two injections ten days apart. Thirty days after the last injection, peritoneal exudates were induced and collected as described above. In addition, the spleens were removed aseptically. Cells of the peritoneal exudates were pooled and washed twice with heparinized Ringer's solution. The packed cells (2.6 ml.) were suspended in 50 ml. of heparinized Ringer's solution containing 10 per cent normal guinea pig serum. Eight milliliters of the cell suspension were injected intraperitoneally into a normal guinea pig. The balance of the cell suspension was subjected to sonic vibration, as described previously, and centrifuged for fifteen minutes at 3,000 r.p.m. Half of the supernate was injected intraperitoneally in 8 ml. amounts into each of 2 normal guinea pigs. The other half was heated to 60°C. for fifteen minutes and then injected in 8 ml. amounts into 2 normal animals. The spleens were pooled and homogenized in 80 ml. of heparinized Ringer's solution in a Waring Blendor. The homogenate was then centrifuged at 2,000 r.p.m. for fifteen minutes and the sediment was suspended in 50 ml. of heparinized Ringer's solution. Half of the suspension was used to inject 3 normal recipient guinea pigs intraperitoneally. The first received 2.5 ml.; the second, 5.0 ml.; and the third, the supernate after centrifugation of 7.5 ml. at 3,000 r.p.m. for fifteen minutes. The other half of the splenic suspension was subjected to sonic vibration and centrifuged for fifteen minutes at 3,000 r.p.m. The supernate was injected intraperitoneally into 3 normal guinea pigs in 2.5, 5.0, and 7.5 ml. amounts.

Twenty-four and forty-eight hours after transfer, all recipient animals were skin tested with 0.1 ml. (5 γ) of PPD. Three and four days after transfer, the recipients which had received peritoneal cells were tested with 0.1 ml. of a 1:4 dilution of deglycerinated OT. Five and six days after transfer, the recipients which had received splenic material were tested with 0.1 ml. of a 1:4 dilution of deglycerinated OT.

RESULTS

The results of the first experiment are presented in table 1. It may be seen that positive reactions to tuberculin (OT) were obtained in recipients which had been injected with extracts of peritoneal cells obtained from sensitized donor

TABLE 1

TUBERCULIN SKIN REACTIONS (FORTY-EIGHT-HOUR) IN RECIPIENT ANIMALS AFTER INTRAPERITONEAL INJECTION OF SONIC-DISRUPTED OR INTACT LEUKOCYTES

Treatment of Leukocytes	Reactions (mm.) to 0.1 ml. 1:4 OT	
	24 Hours After Transfer	48 Hours After Transfer
None	2 × 2	6 × 7
	2 × 3	6 × 8
Sonic	3 × 3	7 × 7
	2 × 2	6 × 8

TABLE 2

TUBERCULIN SKIN REACTIONS (FORTY-EIGHT-HOUR) IN RECIPIENT ANIMALS AFTER INTRAPERITONEAL INJECTION OF SONIC-DISRUPTED (HEATED AND UNHEATED) OR INTACT LEUKOCYTES

Treatment of Leukocytes	Reactions (mm.) to:			
	5 γ PPD		0.1 ml. 1:4 OT	
	24 Hours After Transfer	48 Hours After Transfer	72 Hours After Transfer	96 Hours After Transfer
None	5 × 5	7 × 8	4 × 4	4 × 5
Sonic (30°C.)	5 × 5	4 × 4	4 × 5	4 × 5
	4 × 5	3 × 4	4 × 4	4 × 5
Sonic (60°C.)	0	0	0	0
	0	0	0	0

animals and subjected to sonic vibration. There was no significant difference, in size and characteristics, between these reactions and those obtained in recipients which had received intact, viable peritoneal cells.

The results of the second experiment (tables 2 and 3) demonstrate that heating the extract of peritoneal cells at 60°C. for fifteen minutes destroys its ability to passively transfer tuberculin hypersensitivity. The tuberculin reactions obtained in guinea pigs which received splenic material were less intense than those in the animals which were injected with peritoneal cells (table 3). Two of the 3 animals which received untreated spleen homogenate died forty-eight to seventy-two hours later. These 2 animals appeared to have a delayed type of shock reaction; however, autopsy did not reveal hemorrhagic tissues or fluid in serous cavities such as is commonly seen in tuberculin shock. It is not possible to say whether the animals died as a result of injection with spleen homo-

TABLE 3

TUBERCULIN SKIN REACTIONS (FORTY-EIGHT-HOUR) IN RECIPIENT ANIMALS AFTER INTRAPERITONEAL INJECTION OF SONIC DISRUPTED OR INTACT SPLEEN HOMOGENATE

Treatment of Spleen	Ml. Injected	Reactions (mm.) to:			
		5γ PPD		0.1 ml. 1:4 OT	
		24 Hours After Transfer	48 Hours After Transfer	120 Hours After Transfer	144 Hours After Transfer
Homogenate	2.5	3 × 4	3 × 4	D*	
	5.0	3 × 3	3 × 3	D	
	7.5†	0	0	N.D.‡	N.D.
Sonic extract	2.5	3 × 3	3 × 3	3 × 4	4 × 4
	5.0	4 × 5	4 × 6	4 × 5	4 × 5
	7.5	5 × 6	6 × 8	5 × 5	5 × 6

* D—Died

† Supernatant after centrifugation at 3,000 r.p.m. for fifteen minutes

‡ N.D.—Not done, animal ill

genate *per se*, or as a result of the subsequent tuberculin tests. There were no deaths among the animals which received extracts of sonic-treated spleens. All of these animals demonstrated a delayed type of skin reaction when tested with PPD twenty-four and forty-eight hours after transfer. They still reacted to tuberculin (OT) six days after transfer (table 3).

DISCUSSION

The results of these studies indicate that intact, viable cells are not required to passively transfer tuberculin hypersensitivity in guinea pigs. This suggests that the substance responsible for passive transfer is preformed in the sensitized donor cells. It is possible that sonic vibration frees the active principle from the sensitized cells without altering its transfer capacity. The active principle is probably similar to the antibody described by Cole and Favour (7) in their plasma fraction IV-10 obtained from sensitized guinea pigs.

It is difficult to understand why freezing and thawing of human leukocytes yields an active principle (6), whereas similar treatment of animal leukocytes abolishes their capacity to passively transfer tuberculin sensitivity (1). The present studies throw no light on this problem, but do reveal that treatment of cells of sensitized guinea pigs with sonic vibration does not destroy a substance which can passively transfer tuberculin hypersensitivity. It should be pointed out that Jeter and associates (5) attempted to passively transfer tuberculin hypersensitivity with sonic-treated cells from sensitized guinea pigs, but were unsuccessful. They suggested that their failure may have been due to an inability to achieve a high degree of donor sensitivity.

Studies aimed at the identification of the active principle in extracts of sonic-treated peritoneal cells and spleens of sensitized animals are in progress in this laboratory.

SUMMARY

Sonic vibration of cells of peritoneal exudates or spleen homogenates obtained from sensitized donor guinea pigs yields an extract which is capable of passively transferring tuberculin hypersensitivity to normal recipient animals.

SUMARIO

Transferencia Pasiva de Hipersensibilidad a la Tuberculina en los Cobayos Usando Células Desorganizadas por la Vibración Sónica

La vibración sónica de las células de los exudados peritoneales o de los homogeneados esplénicos obtenidos de cobayos sensibilizados usados como donantes rinde un extracto capaz de traspasar pasivamente hipersensibilidad a la tuberculina a animales normales usados como receptores.

RESUME

Transfert passif de l'allergie tuberculeuse au cobaye par l'emploi de cellules désorganisées par la vibration sonore

La vibration sonore appliquée aux cellules d'exudats péritonéaux ou aux homogénats de rate de cobayes donneurs sensibilisés donne un extrait apte à transférer passivement l'allergie à la tuberculine aux animaux récepteurs normaux.

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ENHANCEMENT OF RESISTANCE TO TUBERCULOSIS IN MICE EXPERIMENTALLY INFECTED WITH BRUCELLA ABORTUS[1]

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INTRODUCTION

A systematic histologic study of organs taken from mice infected with *Brucella abortus* and sacrificed at regular and short intervals throughout the whole course of the disease showed that the local phagocytic cells which had been mobilized during the acute phase of the infection remained in this state for months during the chronic stage of the disease. In the organs of the reticuloendothelial system, particularly in the spleen, the reticular cells appeared hyperplastic and cuffs of monocytes surrounded the ducts and blood vessels; in the lungs the septa appeared more cellular than normally, while thick coats of monocytic cells surrounded the blood vessels and the bronchial tree. On the other hand, similar studies on the development of tuberculosis in mice intravenously infected with bacilli of human type have shown that the phagocytic cells of various organs played a very important role in the defense of the animals against *M. tuberculosis* (1). These two observations suggested a series of experiments designed to determine whether there would be any differences in the reaction to infection with *M. tuberculosis* in mice whose defense system had previously been mobilized by infection with *B. abortus*.

MATERIAL AND METHODS

Ninety mice of both sexes, CF1 strain, were infected with the virulent *B. abortus* strain 2308, and 75 female mice were injected with the avirulent *B. abortus* strain 19[3] which has been widely used for calf vaccination in the United States. The animals were kept in cages in groups of 5 to 10, were fed with Purina pellets, and had free access to water. Inocula were prepared by washing off with 5, 10, or 20 ml. of physiologic saline, the cultures of brucellae incubated for four days on tryptose-agar slants in standard test tubes. These suspensions are designated hereafter as 1:5, 1:10, and 1:20. Mice infected with the virulent strain received 0.2 ml. of the 1:10 or 1:20 suspension of brucellae injected into the peritoneal cavity or into one of the tail veins. The animals injected with the avirulent strain received one, two, or three injections of either 0.1 ml. of a 1:5 suspension, or 0.2 ml. of a 1:10 suspension, subcutaneously, intraperitoneally, intravenously, or intranasally. The intranasal instillation was carried out according to the method first used by A. Monnier in Castaneda's laboratory in Mexico City for the intranasal infection of mice with typhus rickettsiae. The animals were anesthetized with ether and the inoculum instilled into their nostrils. This method was later taken over and popularized by M. Ruiz Castaneda.

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[3] The writer is well aware of the fact that *B. abortus* strain 19 is not completely attenuated for man as would appear from the accidental infection of humans which has been recorded. In mice, however, although a few animals died after repeated doses of the organism, as will be seen in the following paragraphs, at the first injection it was well tolerated in doses at which the fully virulent strain would have killed the animals overnight.

Animals infected with the virulent *Brucella* strain soon became very sick, and many died within a few days or weeks. After six weeks, roughly 25 to 35 per cent of the total number of animals infected had died and the remaining animals were recovering from the disease. Their general condition progressively improved and approximately three months after infection most of them had the appearance of normal animals.

The reaction of mice injected with the avirulent strain depended on the route of infection and on the number of doses of inoculum administered. Subcutaneously injected animals showed little or no reaction; in the group of intravenously and intranasally injected mice, the animals were lethargic for several days but recovered promptly after the first injection. Their reaction to the second and third injections was more severe; and, of the intravenously infected animals, 2 of 20 died after the second, and 2 of 10 died after the third injection; in the group of intranasally infected animals, one of 5 died after the second administration.

These mice were superinfected with *M. tuberculosis* three to ten months after infection with the virulent strain of *Brucella*, or two to four weeks after administration of the avirulent strain. The inoculum was prepared from thirteen-day-old cultures of the virulent H37Rv human strain on Sauton's synthetic medium and resuspended in saline to a final concentration of 1.5 mg. of wet weight per ml. Two-tenths of a milliliter of this suspension was injected into one of the tail veins of each animal. Normal animals infected in this manner died regularly within the third week after infection.

All dead animals were autopsied, the lesions encountered were carefully noted, and the most demonstrative of these were photographed. In selected animals, one lung, the heart, liver, spleen, kidneys, bone marrow, lymph nodes, brain, and hypophysis were taken for histologic examination. To determine whether *Brucella* was present in animals which died with tuberculous lesions, in some experiments the left lung or the pyramidal lobe of the right lung and the spleen of selected animals were cultured in artificial media. Altogether, 40 mice injected with the avirulent strain and 9 mice infected with the virulent strain were culturally examined for brucellae.

The technique used for isolation and identification of *Brucella* was the following: The organs were removed with the usual aseptic precautions, minced with scissors, and placed in tubes containing 10 ml. of tryptose broth (Difco®), and incubated under 10 per cent carbon dioxide at 37° C. for at least four days. Subcultures were then made on tryptose agar plates (with and without 1:700,000 crystal violet). A culture of *B. abortus* strain 19 was included with every series for comparison. After incubation of these plates under carbon dioxide for at least five days, suspicious colonies of Gram-negative rods or coccobacilli were inoculated into Kligler's agar or Friewer-Shaughnessy medium. Non-motile coccobacilli producing hydrogen disulfide and failing to ferment carbohydrates were considered to be *B. abortus*.

TABLE 1

MICE INFECTED WITH VIRULENT BRUCELLA

Number of Mice	Dose	Route	Mortality After Challenge—at Weeks					Survival in Days			Tubercles in Lung—Number of Mice
			3	4	6	9	13	Lowest	Highest	Average	
18	0.2 ml. 1:20 suspension	Intravenous	14	2	1		1	15	49	19	0: (11) +: (1) ++: (2) +++: (2) ++++: (2)
12	Controls		11			1		14	19	17	+++: (1) ++++: (11)

TABLE 2

MICE INJECTED WITH AVIRULENT BRUCELLA

Number of Mice	Dose (1:10 Suspension)	Route	Mortality After Challenge at weeks											Survival in Days			Tubercles in Lung—Number of Mice	Brucella	
			3	4	5	6	7	8	9	10	11	12	15	19	Lowest	Highest	Average		Lung	Spleen
	ml.																			
10	0.2	Intravenous					1	4	4	1					47	64	56	0: (5) ++: (4) +++: (1)	1/8	1/8
7	0.2 × 2 (1 week interval)	Intravenous			2	2		2	1						22	82	45	0: (3) ++: (1) +++: (3)	1/4	1/4
9	0.2 × 3 (1 week interval)	Intravenous			1			2	3		1	1	1		24	99	58	0: (5) ++: (2) +++: (2)	0/6	1/6
10	0.2	Subcutaneous		6	3									1	16	54	30	0: (6) ++: (2) ++++: (2)	1/5	1/5
10	0.2 × 2 (1 week interval)	Subcutaneous		6	1		1	2							17	47	27	0: (3) ++: (3) +++: (4)	1/4	1/4
10	0.2 × 3 (1 week interval)	Subcutaneous		3	3	1					1	1	1		20	77	38	0: (3) ++: (1) +++: (5) ++++: (1)	0/4	0/4
10	Controls			10											16	20	19	+++: (2) ++++: (8)		

In recording the degree of involvement of the lung, the common grading system of 1 to 4 plus is used in this communication (tables 1 to 3). The symbol *4+* designates the classic lesions encountered at the autopsy of untreated intravenously tuberculosized mice; less severe lesions are indicated, according to decreasing intensity, by *3+*, *2+*, or *1+*. As the results were about the same in all series of mice infected with the virulent *Brucella* strain, only one of these experiments is recorded in tabular form (table 1). However, the use of different routes of infection in these animals and variations in the dosage of the avirulent *Brucella* strain make it necessary to tabulate the total number of mice treated with this organism (tables 2 and 3).

RESULTS

Mice Infected with Virulent Brucella

In table 1 data is given on mice infected with virulent *Brucella*. In this group of animals, the survival is not very significant (nineteen days compared with seventeen days for the control mice) if the only mouse which survived as long as thirteen weeks be excluded from appraisal. It may be added, however, that in

TABLE 3

MICE INJECTED WITH AVIRULENT BRUCELLA

Number of Mice	Dose (1:5 Suspension)	Route	Mortality After Challenge at Weeks									Survival in Days			Tubercles in Lung—Number of Mice	Brucella	
			3	4	7	8	9	10	11	14	15	16	Lowest	Highest	Average		Lung	Spleen
	ml.																	
5	0.1	Intranasal			1	2	1			1			43	92	60	0: (5)	0/5	0/5
4	0.1 × 2 (1 week interval)	Intranasal				1		2	1				51	74	63	0: (4)	0/4	0/4
5	0.1	Intraperitoneal					2	1			1	1	56	92	72	0: (2) +: (2) ++: (1)		
5	0.1	Intravenous		3				1					24	92	47	+: (1) ++: (2) +++: (1)		
10	Controls		9	1									15	28	18	0: (1) ++: (2) +++: (2) ++++: (5)		

other experiments the average survival time of a series of 32 animals was twenty-four days compared with seventeen days for the control mice, and in another group of 11 mice it was twenty-four days compared with nineteen days for the control mice. In two small groups of 5 animals each, one group of which had been infected with *Brucella* by the intravenous route and the other intraperitoneally, survival in the former averaged forty-one days and in the latter forty-eight days, compared with nineteen days for the controls. However, the experiment shown in table 1 is remarkable for the fact that 11 of 18 animals (61 per cent) failed to develop tubercles in the lung, while in the other experiments mentioned above tubercles were absent in approximately 50 per cent of the animals.

Mice Injected with Avirulent Brucella

In this series of animals (table 2) the average survival of *Brucella*-infected mice is significantly longer than that of control mice. There is, however, a striking difference, both in the survival and in the severity of the lesions of the lung, between the intravenously and the subcutaneously injected groups of animals. In the intravenous group only a few animals died during the fourth week after challenge, whereas in the subcutaneous group 50 per cent of the mice died during the third week, and two-thirds of the remainder followed during the fourth week after challenge. Repeated doses of *Brucella* seem to have had less influence on the early mortality rate than on the duration of survival of the

animals which escaped early death. The presence of *Brucella* was detected in four lungs and in five spleens of the 31 animals which were examined bacteriologically.[4]

In another series (table 3), as in the previous series, the survival time of *Brucella*-infected animals is significantly longer than that of the control mice. This table provides an even more striking demonstration of the importance of the route of administration of *Brucella* for the final results of the experiment; none of the group of 9 mice in which *Brucella* was administered by the intranasal route developed tubercles in the lungs. In fact, the results shown in table 3 confirm and extend the results shown in table 2.[5]

Clinical Evolution of Disease

The course of the disease depended upon whether the mice were infected with the virulent or the avirulent strain of *B. abortus*. Those previously exposed to the virulent strain remained, like the control mice, in good general condition and continued to gain weight during the first twelve days after infection with tuberculosis. Then they became sick, with dyspnea as the most apparent clinical symptom, and many animals died during the third week after tubercularization. The remaining mice also showed dyspnea, interrupted in most instances by a periodically recurring coughlike spasm, but their general condition was satisfactory during this early phase and their water intake remained unchanged.[6] After a time these animals lost appetite, however, and their weight began to decline, at first irregularly and slightly, later at an almost regular rate of approximately 1 gm. a week. After several weeks, cyanosis appeared which increased progressively and, when the weight of the animals had dropped to less than 20 gm., they showed the typical appearance of tuberculous mice characterized by apathy, hunched back, ruffled hair, dyspnea, and cyanosis. During the following weeks the general condition of the animals deteriorated further, the dyspnea persisted and was continuous in most of the mice, being intermittent in the remainder; cyanosis became still more marked, and the animals died when their weight dropped to approximately 15 gm.

In mice injected with the avirulent strain of *B. abortus*, the clinical picture of the disease developed according to a different pattern. This became apparent twelve days after infection with *M. tuberculosis*, when the control mice became sick while the *Brucella*-infected animals remained in good health and continued to gain weight for another week or two, during which period their water intake was almost unchanged. About a month after challenge with tuberculosis, one or

[4] One of the 10 animals which had received one subcutaneous dose of *Brucella* and which died 132 days after the challenge, in which chronic tuberculous lesions were found microscopically, has been excluded from the table as being an extreme case.

[5] The last mouse of the intravenously infected group did not die and was killed 169 days after infection. Although most interesting slight tuberculous lesions were found in this normal-looking animal, it has not been included in the appraisal of the survival time of this group.

[6] It has been the writer's experience that in mice intravenously infected with *M. tuberculosis* a sudden decrease in the water intake of animals still showing good general appearance heralds the clinical onset of the disease.

2 of 10 animals began to show signs of illness, the principal symptoms of which were dyspnea and loss of weight. As time went on other animals of the series became ill, and after approximately four to five weeks they were all affected to a variable degree but with the same clinical symptoms. Once the first signs of illness had appeared, the disease developed in all of the mice according to the

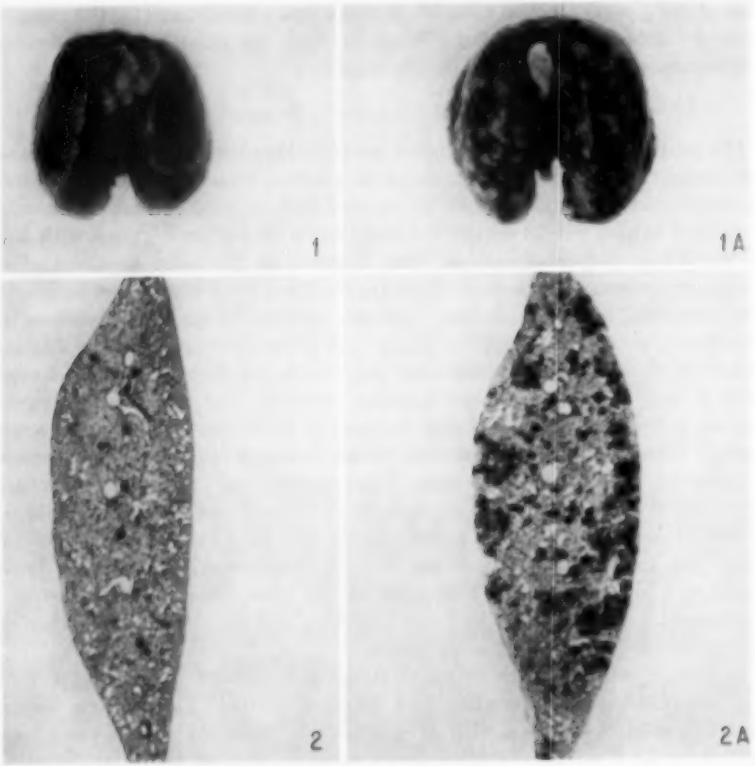

FIG. 1. Lung of mouse infected on February 12, 1954, by intravenous injection of 0.2 ml. of a 1:20 suspension of the virulent *B. abortus* strain 2308 and challenged on April 1, 1954, by intravenous injection of 0.2 ml. of a suspension of tubercle bacilli. Died on April 20 (nineteen days after infection with *M. tuberculosis*). Tubercle-free pneumonia involved the entire lung.

FIG. 1A. Lung of control mouse infected on April 1, 1954, by intravenous injection of 0.2 ml. of a suspension of tubercle bacilli; died on the same day as previous animal. The lung is studded with tuberculous nodules.

FIG. 2. Low-power magnification of a cross section of the left lung of mouse which was infected with brucellosis and with tuberculosis at the same time as the first animal, and which also died nineteen days after tubercularization. No trace of tubercles. (×11)

FIG. 2A. Low-power magnification of a cross section of left lung of another control mouse of the same series, which died on the same day as the previous control animal. The left lung was sprinkled with tubercles. (×11)

pattern which has already been described for the group of mice infected with the virulent strain of *B. abortus* which escaped early death.

Post-Mortem Findings

Macroscopic examination: At autopsy, in the *Brucella*-infected animals as in untreated control mice, the lungs were found to be the most severely involved of all of the organs, but the lesions were significantly less severe than in the control animals.

In approximately 50 per cent of the mice, the lungs showed only congestion combined with consolidation, which was patchy in animals injected with the avirulent strain and diffuse in those infected with the virulent strain of *B. abortus* (figure 1). The lungs of the remaining mice were also congested and partly consolidated but, in addition, they were studded with a variable number of tubercles which were, however, less numerous than is generally observed in the lungs of untreated control mice. In only a small minority (approximately 5 per cent) of the animals were the tubercles as numerous as they were in the lungs of control mice, one of which is shown in figure 1*A*. Besides being less numerous, the tuberculous nodules were usually smaller and, because of their cloudy appearance, less well defined than in control mice. Unlike the tubercles in untreated mice, many of which are superficial (figure 1*A*) and protrude into the pleural cavity and give the lung a granular appearance, in *Brucella*-infected mice the nodules were located in the deep layers of the lung parenchyma leaving the pleura thin, smooth, translucent, and glistening. Regardless of the type of lesion encountered in individual animals, both lungs were regularly involved and showed the same alterations in type, localization, severity, and extent.

Of the other organs, the spleen was frequently moderately enlarged in mice infected with the virulent strain of *Brucella* without ever showing any tuberculous lesions; it was almost regularly of normal size in mice treated with avirulent

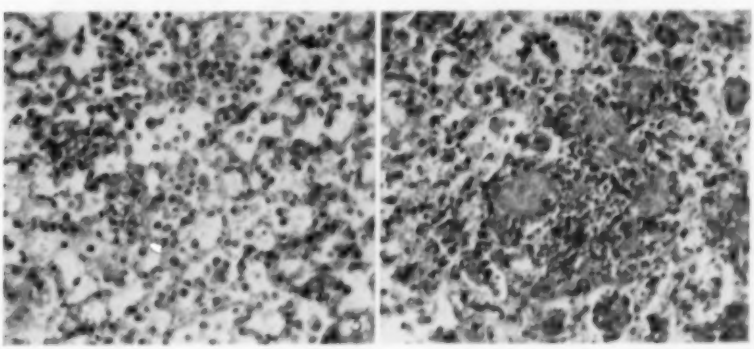

FIG. 3. Fragment of figure 2 seen at higher magnification. Congestion, thickening of the alveolar septa, alveoli filled with scant exudate mixed with desquamated lining cells and a few leukocytes. (Hematoxylin and eosin, ×300)

FIG. 3*A*. Higher magnification of a fragment of figure 2*A*, showing one of the tuberculous nodules. (Hematoxylin and eosin, ×300)

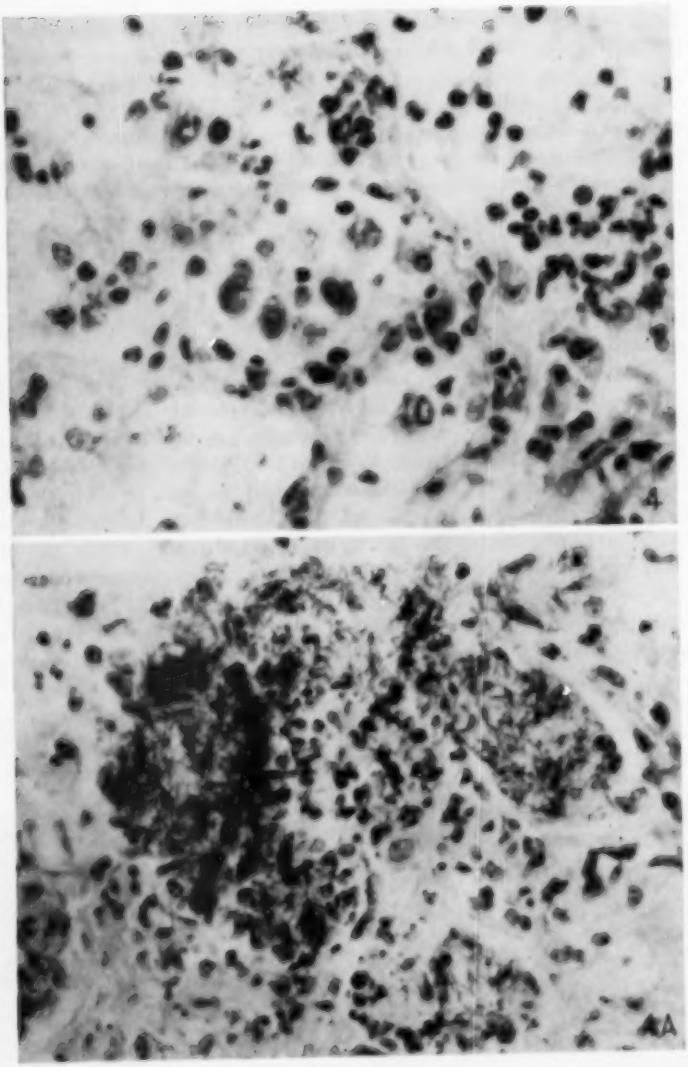

FIG. 4. Fragment of the lung shown in figure 2. Alveoli filled with desquamated lining cells and leukocytes containing a few bacilli. (Ziehl-Neelsen counterstained with hematoxylin, ×800)

FIG. 4A. High-power magnification of one of the tuberculous nodules shown in figure 2A, consisting of necrotic masses and cellular debris interspersed with numerous bacilli. (Ziehl-Neelsen counterstained with hematoxylin, ×800)

Brucella. The liver showed no noteworthy alterations, but the kidneys of some animals contained yellowish-white, slightly translucent foci the size of millet seeds. On the cut surface of some of these kidneys, macroscopically visible necrotic foci which were the size of a large pinhead could be distinguished. The lymph nodes showed no alterations.

Microscopic findings: A detailed account will be reported elsewhere of the development of tuberculosis in *Brucella*-infected mice, giving findings on animals which were killed during the initial stages of the evolution of the tuberculous infection at hourly, and later at daily, intervals and including almost all animals which died several months after challenge. However, in order to make the present study more complete, it seems advisable to outline briefly the main histologic features.

In most of the consolidated lungs without tubercles observed in mice which had been infected with the virulent *Brucella* strain (figure 2) the septa were thickened and the alveolar spaces were filled with fibrin and with swollen, desquamated alveolar cells, containing a variable but always moderate number of bacilli in areas interspersed with leukocytes (figures 3 and 4). In some of these lungs a few alveoli, usually located in the deep layers of the organ, were filled with degenerating or degenerated alveolar cells, disintegrated leukocytes, and fairly numerous bacilli.

In almost all tubercle-free lungs, small groups of alveoli were present which were filled with degenerating cells characterized by small nuclei, many of which were in lysis, and by a considerably swollen and faintly stained cytoplasm with or without bacilli; a few of these cells filled, and often even distended, the alveolar spaces involved.

In mice which had been injected with the avirulent strain, the pneumonic lesions broadly resembled those observed in mice infected with the virulent *Brucella*, with the difference, however, that exudate was either scanty or altogether absent. In lungs with tubercles, the nodules were smaller and far less necrotic. In almost all of the lungs examined, desquamated alveolar cells and phagocytes containing bacilli were found in the bronchi. In a few instances the bronchial tree was filled with these cells.

In the organs of the reticuloendothelial system of both groups of animals, there were a few small groups of reticular cells or of leukocytes containing a few bacilli. Large numbers of bacilli were found only in the kidneys of a few animals; they appeared in the form of aggregates filling some of the glomeruli or in clumps, some of which appeared to be floating freely in the tubules, while others were located in intertubular spaces and were surrounded by numerous phagocytes, mainly of the mononuclear type. Not infrequently tubules were found in the medulla which were considerably distended by masses of leukocytes containing phagocytized bacilli.

DISCUSSION

The results presented above indicate that a preceding *Brucella* infection renders mice resistant to a subsequent infection with *M. tuberculosis*. The increased

resistance of the animals to tuberculous infection manifests itself by a lesser number or by the absence of tubercles in the lung and by a prolonged survival time after the challenging infection. There is a striking difference, however, in the resistance induced by the virulent and that elicited by the avirulent *Brucella abortus*. From the series of animals recorded in table 1 it appears, indeed, that the protective action of the virulent *Brucella* manifests itself less in the survival time than in the development of milder lesions in the lungs. Other experiments of the same type recorded in previous paragraphs bear evidence, however, that the virulent *Brucella* can also induce a significant increase of the survival time, which varies, however, in different groups of animals.

More demonstrative are the results observed in the series of mice injected with the avirulent strain of *Brucella*. In the two experiments recorded in tables 2 and 3, the survival of the animals was significantly longer, and the lesions of the lungs milder, than in control mice. Moreover, variations in the length of survival time between the different groups of mice were less pronounced than in the series of animals infected with the virulent strain of *Brucella*.

Most important is the observation that, in the series of animals infected with the virulent as well as in those injected with the avirulent strain of *Brucella*, the degree of protection conferred varied considerably according to the route of infection. Subcutaneously injected animals were the least resistant, the intraperitoneal route gave better results, and the best protection was provided by the intravenous and intranasal routes of administration of *Brucella*.

Repeated administrations of *Brucella* did not increase the resistance of the animals to any striking degree; how far the dosage of *Brucella* influences the resistance remains to be determined. It may be added that for the animals infected with virulent *Brucella* recorded in this study the dose was calculated to produce significant lesions in the organs during the acute phase of the infection and to leave a reasonable number of animals alive for the study of chronic brucellosis. The animals which were injected with the avirulent strain of *Brucella* were given the largest possible number of organisms with the notion that this might confer a better protection.

The less severe lesions of the lungs were accompanied by a milder clinical course of the disease. Generally speaking, it may be said that, instead of the fulminating tuberculosis resulting from infection by the intravenous route observed in control mice, *Brucella*-infected animals develop a protracted form of the disease, characterized by delayed onset which, moreover, does not appear simultaneously in all animals, by dyspnea with cyanosis, and by a slow but uninterrupted loss of weight. As a result the animals succumb to the disease but, whereas control mice die regularly within three weeks, *Brucella*-infected animals die within three months after challenge with tubercle bacilli. Since the general symptoms of the disease are similar in both groups of animals, apart from the dyspnea which is more regularly observed in *Brucella*-infected mice, the tuberculosis which develops in *Brucella*-infected mice may be compared to a slow motion picture of the acute disease which develops in control mice.

The observation that the avirulent *Brucella* confers a better protection than the virulent organism might be a phenomenon of great significance, but it is difficult to find a satisfactory explanation of its nature. Two possibilities may be taken into account. First, a latent infection by the virulent *Brucella* might be reactivated by the challenging infection with tuberculosis and contribute to increasing the mortality rate of the animals; second, the remarkable resistance of mice injected with the avirulent strain might be due to the amount of *Brucella* administered, which was from two to four times larger than that of the virulent *Brucella*.

The first hypothesis cannot be accepted because intravenously introduced *Brucella* gives fairly characteristic focal lesions in the lung, but never a diffuse pneumonia as was found in the series of animals shown in table 1. Moreover, *Brucella* only exceptionally become trapped in the lung, as has been shown by bacteriologic examination of the lungs of other series of animals. Finally, the histologic examination of all of the lungs of the series showed the tuberculous nature of the pneumonia.

As for the second hypothesis, since repeated doses seemed to have had some bearing on the degree of resistance of the animals, the possibility exists that the dosage of *Brucella* is an important factor in the induction of the resistance of mice to tuberculosis. The final answer to this question might be provided by further experiments.

The profound alteration in the pathology of the tuberculous pneumonia which develops in mice treated, prior to tubercularization, with *B. abortus*, the salient characteristic of which is a lesser number of tubercles or absence of the nodules, is certainly a finding of considerable interest. It may be assumed that it is closely connected with the marked alteration induced in the phagocytic system of the mouse by the preceding brucella infection. No attempt will be made in the present report to explain the process, which is most probably intimately related to the still much debated question of the significance of the tubercle in the resistance of the organism to *M. tuberculosis*. A detailed histologic study of lungs of *Brucella*-infected and subsequently tubercularized mice, in which the development or absence of tubercles can be induced experimentally, might provide much valuable information about this most controversial problem. The task would be singularly eased if further experiments confirm the most interesting observation recorded in this report (table 3) and show that tubercle-free pneumonia regularly develops in mice which have been infected with *Brucella* by the intranasal route.

Whatever the significance of the absence of tubercles in the pathology of tuberculosis may be, there can be no doubt that it is a beneficial phenomenon. Tubercles in mice sooner or later undergo necrosis, and the involved portions of the lungs are destroyed. It follows that tuberculosis coursing without tubercles is less destructive, and therefore less severe, than the classic disease which develops in untreated mice. A further implication of the absence of tubercles could be of prime importance in any chemotherapeutic attempts, for there is

good reason to believe that certain antimicrobial drugs are compromised in their effectiveness within a patch of necrotic tissue deprived of blood supply and teeming with bacilli (figure 4*A*), such as were noted in the lungs of untreated mice (figures 1*A* and 2*A*). Such difficulties might be overcome by means of procedures inducing tuberculous lesions like the one shown in figure 4.

Taking into account the less severe lesions and the longer survival of *Brucella*-infected mice, it is difficult to escape the conclusion that they are more resistant to tuberculosis than normal mice. It is not easy to determine the mechanisms involved, but some speculation as to their nature is in order. The first possibility which comes to mind is that the resistance could be due to interference between the two microorganisms, *B. abortus* and *M. tuberculosis*, in a manner similar to the well-established interference phenomenon which occurs between different viruses. However, bacteriologic examination of the spleen and lungs of 31 mice in the series of animals infected with the avirulent strain suggests that the presence or absence of brucellae is not related to the animal's resistance to tuberculosis. This would seem to appear from the fact that, while 6 of the 7 mice recorded in table 2 (86 per cent) which had positive *Brucella* cultures prepared from the lung or the spleen, or from both, had no pulmonary nodules, 18 of the 24 *Brucella*-negative animals (75 per cent) showed lungs likewise free of tubercles. Even more suggestive in this respect is the observation that the entire group of 9 mice which were intranasally infected with the avirulent strain, and of which none had developed tubercles, showed cultures negative for *Brucella* from both the lungs and the spleen (table 3). In further support of this same view, it should be noted that 5 animals infected intravenously with the virulent *Brucella* strain were all negative when cultured for this organism and none of them showed tubercles at autopsy. On the other hand, in many of the mice infected with the virulent strain which did develop numerous tubercles in the lungs, masses of brucellae have been found in lesions of the kidneys and the testicles. Moreover, in one instance, extensive necrotic lesions containing great numbers of brucellae co-existed with fairly severe tuberculous lesions of the lung.

If there is any evidence that there existed some kind of interference between *B. abortus* and *M. tuberculosis* it would be rather that the tubercle bacilli interfered with the presence of brucellae, at least in the two organs which have been examined bacteriologically, i.e., the lung and the spleen. This opinion is based on the observation that the lungs and the spleens of 9 of 10 animals infected with the virulent strain and examined bacteriologically were found to be negative for *Brucella*. In the experience of the writer, with brucellae in organs of mice which had been infected with heavy doses of these organisms, it has never been observed that in any such group almost all of the animals were negative for *Brucella* even when they were sacrificed more than a year after infection. That *M. tuberculosis* does interfere with the development of other microbes is suggested by the very small number of contaminants present in the lungs of mice which die in the terminal stage of the disease. Despite the extensive destruction of the lung, which would seem to be a suitable culture medium for saprophytic bacteria, contam-

inants are so few that in the writer's experience uncontaminated cultures of *M. tuberculosis* on Sauton's synthetic medium are obtained directly from such lungs. Suspensions of tuberculous lungs grown on either liquid or solid ordinary media yield only occasionally one or a few colonies of contaminants, while in most instances they remain free of bacterial contamination.

The results observed might also be due to some type of induced "immunity." This hypothesis finds some support in the following observations:

Most of the bacilli were within phagocytic cells. As contrasted with the control mice, in *Brucella*-infected animals the host cells, including the alveolar cells of the lung, did not disintegrate under the influence of the bacilli harbored in their cytoplasm but, on the contrary, appeared to inhibit the growth of the bacteria.

The route used for infecting the animals with brucellosis was a critical factor in inducing resistance to *M. tuberculosis*, exactly as it is in experiments designed to elicit humoral immunity in mice to viruses, an observation which has been made by Dr. Herald R. Cox (2).

The dosage of brucellae administered to the mice seemed to play a fairly important role in the development of resistance to tuberculosis of the animals.

The time interval between the last injection of brucellae and the date of challenge of the animals with tubercle bacilli seemed also to have some bearing on the development of resistance to *M. tuberculosis*. This is suggested by the series of the 5 intravenously injected animals recorded in table 3 which were challenged with tubercle bacilli two weeks after the injection of brucellae. Three of these mice died soon after infection with tuberculosis, whereas in all other experiments in which the challenge came at least four weeks after the administration of brucellae, intravenously injected mice had acquired a good protection.

Another observation worth emphasizing in this connection is the fact that the resistance to tuberculosis of *Brucella*-infected mice does not appear to decrease with time, since 5 animals which had been challenged 283 days after infection with the virulent strain of *Brucella*, showed even better protection than mice challenged at a shorter interval. The possibility exists, it must be conceded, that the remarkable resistance of these animals is to some extent due to their increased age, but neither age nor weight differences would seem to account for the long survival of the entire group of animals. This view is based on the observation, made in our laboratory and also by others, that older mice are only slightly more resistant to tuberculosis than the six- to eight-week old animals used for routine work.

Finally, it is noteworthy that the resistance could be elicited not only by the virulent *B. abortus* strain 2308, but also by the avirulent and immunizing *B. abortus* strain 19.

Much more information is needed to substantiate the hypothesis that the resistance to tuberculosis enhanced by brucella is in some way related to conventional concepts of immunity. The findings of the present study suggest that the resistance of *Brucella*-infected mice to *M. tuberculosis* is due to the action of the local phagocytic cells of the organs and to that of the circulating phagocytes. These cells ingest the bacteria, presumably inhibit their multiplication, and may serve to eliminate them from the infected animals. Evidence in support of these concepts is demonstrated by the presence of masses of leukocytes with phagocytized bacteria filling the bronchial tree of the lung and the cystlike dilatations of the kidneys which have been observed in histologic sections. These observations suggest a cellular rather than a humoral immunity.

In the absence of any known antigenic relationships between *B. abortus* and *M. tuberculosis*, this "immunity" may possibly be related to the biologic properties which the two microorganisms have in common, viz., their affinity for the reticuloendothelial system and their ability to multiply within phagocytes, and to deep changes induced in the cellular defense system by the brucella infection. That these changes are not purely quantitative and exclusively due to the hyperplasia of the local phagocytic system of the organs, but also qualitative, is evidenced by the example of the alveolar cells of the lungs of *Brucella*-infected mice, which are capable of inhibiting the growth of the bacteria, whereas alveolar cells of untreated mice are destroyed by the organisms. It could be rewarding to go deeper into the investigation of the problems under discussion, which might bring out valuable information about immunity in chronic infectious diseases, which has not been nearly as well explored as in acute infections. A contribution to such a study has been made by the recent finding that *B. suis* renders guinea pigs more resistant to infection by the rickettsiae of Q fever (3).

SUMMARY

Mice injected with *B. abortus* are more resistant to tubercle bacilli than control mice. The avirulent strain 19 of *Brucella abortus* provides better protection than the virulent strain 2308. The route of administration of *Brucella* influences greatly the degree of resistance of the animals. The resistance to *M. tuberculosis* of the animals manifests itself by milder clinical symptoms, less severe lesions in the lungs, and a longer survival time. The mechanism by which this resistance is brought about is not known but it is postulated that it might be due to inhibition of the growth of the tubercle bacilli by the phagocytes from the *Brucella*-infected animals.

SUMARIO

Realce de la Resistencia a la Tuberculosis en Ratones Infectados Experimentalmente con Brucella Abortus

Los ratones inyectados con *B. abortus* son más resistentes a los bacilos tuberculosos que los testigos. La cepa avirulenta 19 suministra mejor protección que la virulenta 2308.

La resistencia de los animales al *M. tuberculosis* se traduce por síntomas clínicos más leves, lesiones menos graves en el pulmón y período más largo de sobrevivencia.

No se conoce el mecanismo que interviene en esta resistencia, pero se presupone que podría deberse a inhibición de la proliferación de los bacilos tuberculosos por los fagocitos procedentes de los animales infectados por brucelas.

RESUME

Renforcement de la Résistance à la Tuberculose chez des Souris Infectées Expérimentalement avec Brucella Abortus

Les souris inoculées avec le *B. abortus* sont plus résistantes aux bacilles tuberculeux que les souris témoins. La souche avirulente 19 assure une meilleure protection que la souche virulente 2308.

La résistance de ces animaux au *M. tuberculosis* se manifeste par des symptômes cliniques plus légers, des lésions moins sévères dans le poumon et un temps de survie plus long.

Le mécanisme qui conditionne la résistance n'est pas connu, mais l'hypothèse d'une action inhibitrice des phagocytes d'animaux infectés par la Brucella sur le développement du bacille tuberculeux est formulée.

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VIRULENCE FOR GUINEA PIGS OF TUBERCLE BACILLI ISOLATED FROM PULMONARY LESIONS RESECTED DURING CHEMOTHERAPY[1]

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INTRODUCTION

Observations on the virulence of tubercle bacilli resistant to isoniazid and certain other drugs indicate that many isoniazid-resistant cultures become partially or completely attenuated, as measured by ability to produce progressive tuberculosis, when inoculated subcutaneously into guinea pigs (1–8). This phenomenon has been noted both in stock cultures made resistant by serial transfer in isoniazid-containing medium and in isoniazid-resistant cultures obtained from patients under treatment with the drug.

The present report concerns the relationship between drug resistance and virulence for guinea pigs of tubercle bacilli obtained directly from resected pulmonary tuberculous lesions.

MATERIAL AND METHODS

The tuberculous pulmonary lesions resected from 8 patients provided the material for this study. All 8 had received isoniazid, either alone or along with other drugs, for five to seventeen months. In one patient isoniazid had been discontinued nine months prior to resection; the other 7 were still receiving isoniazid along with other drugs at the time of resection.

In general, larger lesions were studied individually and smaller lesions were pooled. Direct smears were made in most instances. Each lesion (or group of lesions) was removed aseptically from the resected pulmonary tissue and homogenized in a sterile Tenbroeck glass tissue grinder, using sterile physiologic saline as a diluent. The homogenate was processed as follows:

Guinea Pig Inoculation of Homogenate

One half of the homogenate was inoculated subcutaneously in the inguinal region of guinea pigs. Surviving animals were sacrificed three months after inoculation. Virulence was graded according to the scale recommended by Steenken and Wolinsky (2) as follows:

Good: Generalized disease of the lungs, liver, spleen, and lymph nodes.

Fair: Gross disease of the internal organs but less extensive than in the previous category, and no deaths from tuberculosis.

Slight: A local abscess at the site of inoculation with caseation of the inguinal and iliac lymph nodes, but no more than an occasional tubercle in the liver and spleen.

None: No evidence of tuberculosis anywhere in the body, or at the most, a small local abscess with no involvement of the regional lymph nodes.

Culture of Homogenate

The second half of the homogenate was cultured on five tubes of American Trudeau Society (ATS) medium (9). The streptomycin, para-aminosalicylic acid (PAS), and iso-

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niazid susceptibilities of the positive cultures were respectively determined by inoculating 0.2 ml. of the adjusted suspension (approximately three hundred million organisms per ml.) on ATS medium containing graded concentrations of the drug. Readings were made after twenty-eight days' incubation at 37°C., and degrees of drug susceptibility were defined as follows:

Susceptible: No appreciable growth on medium containing 3.5 γ of streptomycin, 1.0 γ of PAS, or 0.2 γ of isoniazid per ml. as compared with growth on the control tube.

Slightly resistant: Growth equal to or only slightly less than the control tube containing 3.5 γ of streptomycin, 1.0 γ of PAS, or 0.2 γ of isoniazid per ml., but no appreciable growth in the tubes containing 15 γ of streptomycin, 10 γ of PAS, or 1.0 γ of isoniazid per ml. of medium.

Moderately resistant: Growth equal to or slightly less than the control containing 3.5 and 15 γ of streptomycin, 1.0 and 10 γ of PAS, or 0.2 and 1.0 γ of isoniazid per ml., but no appreciable growth in the tubes containing 200 γ of streptomycin, 100 γ of PAS, or 5.0 γ of isoniazid per ml. of medium.

Highly resistant: Growth equal to or slightly less than the control on medium containing 3.5, 15, and 200 γ of streptomycin, 1.0, 10, and 100 γ of PAS, or 0.2, 1.0, and 5.0 γ of isoniazid per ml.

Subsequent animal inoculations of suspensions of positive cultures were made to measure the difference in virulence, if any, between the microorganisms cultured on the artificial medium and those present in the original tissue homogenate. Each animal was inoculated with 0.5 ml. of a culture suspension adjusted to contain approximately three hundred million organisms per ml. Macroscopic evidence of tuberculosis was always confirmed by culturing lymph nodes adjacent to the site of inoculation and spleens of all inoculated guinea pigs. In those animals showing no macroscopic evidence of tuberculosis, the spleen was cultured to exclude further the possibility of latent tuberculous involvement. Isoniazid susceptibility tests were performed on tubercle bacilli recovered by culture from guinea pig organs.

RESULTS

In table 1 may be seen the results of direct microscopy, culture, and animal inoculation of 27 lesions obtained from 8 patients at operation. It will be noted in table 1 that 22 of 27 lesions were positive by microscopy and culture; 16 of 27 were positive by guinea pig inoculation, and 7 were negative. Guinea pig inoculations were not made with 4 of the 27 lesions.

In table 2 are shown the drug susceptibility and virulence for guinea pigs of tubercle bacilli isolated from resected lesions. It will be noted in table 2 that tubercle bacilli isolated from 14 of the 22 lesions showed some degree of resistance to all three drugs; two were resistant to isoniazid and PAS, and susceptible to streptomycin; one was resistant to isoniazid and streptomycin, and susceptible to PAS; five showed resistance to streptomycin and PAS, and susceptibility to isoniazid.

In 20 of the 22 lesions positive on culture, the original homogenate had been inoculated subcutaneously into guinea pigs. The animals inoculated with 16 of these lesions showed localized disease (slight virulence) and those inoculated with the remaining 4 lesions showed no disease (no virulence). The cultures which had been obtained from the homogenate of these latter 4 lesions on ATS medium yielded heavy growth (4+), moderate growth (3+), rare (1+), and a single colony, respectively.

TABLE 1

RESULTS OF MICROSCOPY, CULTURE, AND ANIMAL INOCULATION OF 27 LESIONS OBTAINED FROM 8 PATIENTS AT OPERATION

	Number		
	Positive	Negative	Not Done
Open* lesions (11)			
Smear	9	1	1
Culture	11	0	0
Guinea pig	8	2	1
Closed† lesions (14)			
Smear	11	2	1
Culture	9	5	0
Guinea pig	6	5	3
Other‡ (2)			
Smear	2	0	0
Culture	2	0	0
Guinea pig	2	0	0

* Open cavities.

† Solid necrotic lesions or filled-in cavities.

‡ Mucoid material from major bronchus.

For comparison, additional guinea pigs were inoculated with suspensions of tubercle bacilli isolated from the lesions by culture on ATS medium in order to measure the difference in virulence, if any, between these cultures and the original tissue homogenate. The dose of the inoculum was adjusted to approximately one hundred and fifty million organisms per animal. As shown in table 2 under the column headed, "Bacillary Suspension," tubercle bacilli isolated from 20 of 22 lesions showed slight virulence, one showed fair virulence, and one produced no disease in guinea pigs.

The lymph nodes adjacent to the site of inoculation were removed from the group of 16 guinea pigs showing slight virulence on direct inoculation of tissue homogenates. All were positive for acid-fast bacilli on microscopy, and tubercle bacilli were recovered by culture. The tubercle bacilli recovered from these nodes were tested *in vitro* for their isoniazid susceptibility and gave approximately the same results as the original culture. The lymph nodes adjacent to the site of inoculation in the 21 of 22 guinea pigs inoculated with culture suspensions were treated similarly, and identical observations were made.

In addition, the spleens from all guinea pigs were cultured, whether or not gross tuberculous lesions were visible. In the group of animals inoculated with tissue homogenate, all were negative except one. This animal had a tuberculosis index of 4, since the spleen was slightly enlarged and showed a single lesion macroscopically. In the group of guinea pigs inoculated with bacillary suspensions, tubercle bacilli were isolated from the spleen of the guinea pigs which showed an index of 4.0 and 11.5. Cultures of all of the other animals in this group were negative.

The chemotherapy regimens and bacteriologic findings for each patient are

TABLE 2

VIRULENCE FOR GUINEA PIGS AND DRUG SUSCEPTIBILITY OF TUBERCLE BACILLI RECOVERED FROM 22 RESECTED LESIONS

Lesions	Number	Drug Susceptibility*		Index of Tuberculosis†	
		Resistant	Susceptible	Homogenates	Bacillary Suspension
Open (11)	5	Isoniazid, PAS, streptomycin	—	‡,1.5,2.0,none, 2.0	2.0,1.5,2.0,1.0, none
	3	Streptomycin, PAS	Isoniazid	1.0,2.0,1.5	1.0,1.0,1.5
	1	Streptomycin, isoniazid	PAS	1.0	1.5
	2	PAS, isoniazid	Streptomycin	2.0,none	1.5,1.0
Closed (9)	7	Isoniazid, PAS, streptomycin	—	1.5,1.5,1.5,1.0, none,4.0,1.5	1.5,1.5,1.5,4.0, 1.5,1.5,2.0
	2	Streptomycin, PAS	Isoniazid	‡,none	11.5,2.0
Bronchus (2)	2	Isoniazid, PAS, streptomycin	—	2.0,2.0	2.0,2.0

* *See* text for method of performing susceptibility tests and definition of degrees of susceptibility.

† Based on maximum of 16 for each animal: lungs, liver, spleen, and lymph nodes, each assigned a value of 0 to 4, depending on amount of macroscopic tuberculous disease.

‡ Not done.

presented in detail in table 3. As shown in table 3, 7 of 8 patients had received isoniazid in various multiple-drug regimens for seven to seventeen months up to the date of resection. One patient, W.H., had received isoniazid for five months but, because of emergence of isoniazid-resistant tubercle bacilli in sputum specimens, streptomycin and PAS were substituted for isoniazid during the nine months prior to resection.

The well-recognized phenomenon that tubercle bacilli isolated from different lesions in the same patient may vary in their degree of susceptibility to drugs (10, 11) (*cf.* patients B.H., C.L., J.D., and H.T.) is also demonstrated by the data in table 3.

Although tubercle bacilli recovered from all patients were resistant to one or more drugs, there was no direct correlation between the guinea pig virulence and the degree of resistance to any specific drug (*cf.* patients C.L., M.H., and H.T.). In the case of W.C., no studies of guinea pig virulence were made before the start of isoniazid therapy. The possibility that this patient's strain of tubercle bacilli was of low virulence for the guinea pig before treatment, though a typical strain of *M. tuberculosis* in other respects, cannot be entirely excluded. On the basis of work now in progress in this laboratory, however, this possibility is considered remote.

The presence of isoniazid-susceptible organisms of low virulence for the guinea pig has been sought at this hospital in a group of 106 patients with no prior isoniazid therapy, but such strains were found in only 3 patients. In all 3 patients

TABLE 3

CHEMOTHERAPY REGIMENS AND BACTERIOLOGIC FINDINGS IN RESECTED LESIONS OF 8 PATIENTS

Patient	Preoperative Chemotherapy	Lesion	*In Vitro* Susceptibility*			Homogenates		Bacillary Suspension	
			Isoniazid	Streptomycin	PAS	Index of Tuberculosis†	Virulence‡	Index of Tuberculosis†	Virulence‡
B.K.	Isoniazid + streptomycin + PAS, 7 months; two courses of streptomycin + PAS, 3 months and 5 months	Number 4. Four small necrotic foci from wedge, apex, RLL	Susceptible	Highly resistant	Moderately resistant	—§	—	11.5	Fair
		Number 5a. 3.0 × 0.8 × 0.8 cm. unsloughed focus with softened central core, apex, RLL	Highly resistant	Highly resistant	Highly resistant	1.5	Slight	1.5	Slight
		Number 6. Swab of spillage around hilum, RUL	Highly resistant	Highly resistant	Highly resistant	—	—	2.0	Slight
		Number 7. 1 cm. filled-in cavity posterior segment, RUL	Highly resistant	Highly resistant	Highly resistant	1.5	Slight	1.5	Slight
		Number 9a. 1.2 cm. filled-in cavity, apex, RUL	Moderately resistant	Highly resistant	Moderately resistant	1.5	Slight	1.5	Slight
W.H.	Isoniazid, 5 months and none, 9 months preoperatively; streptomycin and PAS, 9 months	Number 3. 1.5 cm. open clean walled lesion, RUL	Highly resistant	Highly resistant	Slightly resistant	1.5	Slight	1.5	Slight
		Number 4. Two 1.0 cm. open clean walled lesions, RUL	Moderately resistant	Highly resistant	Susceptible	1.0	Slight	1.5	Slight
C.L.	Isoniazid, 11 months; isoniazid + streptomycin, 6 months; streptomycin, 50 days; two courses streptomycin and PAS, 3 months and 10 months	Number 1. Occluded material in apical segment of bronchus	Slightly resistant	Moderately resistant	Moderately resistant	2.0	Slight	2.0	Slight
		Number 3. 1.5 cm. open cavity, RUL	Moderately resistant	Susceptible	Moderately resistant	2.0	Slight	1.5	Slight
		Number 4. 2.5 cm. open, dirty cavity, RUL	Moderately resistant	Moderately resistant	Moderately resistant	2.0	Slight	2.0	Slight

M.H.	Isoniazid + PAS, 14 months; two courses streptomycin, 3 months and 43 days	Number 2a. 1.0 cm. filled-in cavity, posterior segment, RUL	Slightly resistant	Highly resistant	Slightly resistant	1.0	Slight	4.0	Slight
W.C.	Isoniazid + streptomycin + PAS, 12 months; streptomycin + PAS, 14 months	Number 1. Two pooled 7 mm. necrotic foci, basal segment, LLL	Slightly resistant	Moderately resistant	Slightly resistant	None	None	1.5	Slight
		Number 3. Wedge of lung tissue of prenecrotic pneumonia, LUL	Susceptible	Moderately resistant	Slightly resistant	None	None	2.0	Slight
		Number 4. Swab of open lesion, LUL	Susceptible	Moderately resistant	Slightly resistant	1.0	Slight	1.0	Slight
		Number 5. Swab of wall of open lesion, LLL	Susceptible	Moderately resistant	Moderately resistant	2.0	Slight	1.0	Slight
J.D.	Isoniazid, 12 months; two courses streptomycin + PAS, 7 weeks and 5 months; streptomycin, 3 months	Number 3. 2.5 cm. open cavity	Highly resistant	Slightly resistant	Highly resistant	None	None ‖	1.0	Slight
		Number 3a. Portion of cavity wall	Moderately resistant	Susceptible	Slightly resistant	None	None	1.0	Slight
L.P.	Isoniazid, 11 months; streptomycin + PAS, 22 months	Number 1. 3 × 2 cm. open, dirty cavity, RUL	Highly resistant	Highly resistant	Moderately resistant	2.0	Slight	None	None
H.T.	Isoniazid, 15 months; streptomycin, 42 days; streptomycin + PAS, 18 months	Number 1. Mucopurulent material major bronchus	Highly resistant	Highly resistant	Highly resistant	2.0	Slight	2.0	Slight
		Number 2. 2.0 cm. softened focus, RML	Moderately resistant	Highly resistant	Highly resistant	4.0	Slight	1.5	Slight
		Number 3. 2.0 cm. softened focus, RLL	Slightly resistant	Highly resistant	Highly resistant	1.5	Slight	2.0	Slight
		Number 4. Area of tuberculous pneumonia	Susceptible	Highly resistant	Highly resistant	1.5	Slight	1.5	Slight

* *See* text for definition of degrees of susceptibility.
† Based on maximum of 16: lungs, liver, spleen, and lymph nodes, each assigned a value of 0 to 4, depending on amount of macroscopic tuberculous disease.
‡ *See* text for definition of degrees of virulence.
§ Not done.

there had been prior chemotherapy with streptomycin-PAS and the tubercle bacilli in the sputum, while isoniazid-susceptible and of low virulence for guinea pigs, were resistant to streptomycin, to PAS, or to both drugs. Moreover, although direct inoculation of the sputum concentrate failed to produce extensive disease in guinea pigs, additional guinea pigs inoculated with suspensions of isoniazid-susceptible organisms obtained by culture from the sputum of 2 of these patients prior to isoniazid therapy showed generalized tuberculosis within three months. The sputum culture of the third patient referred to was not available for further guinea pig virulence study. On the other hand, in the case of H.T., tests performed during the fourth week of isoniazid therapy showed the organisms in his sputum cultures to be both isoniazid-susceptible and highly virulent for guinea pigs, indicating that the change in virulence occurred during isoniazid therapy.

A decrease in virulence for guinea pigs should not suggest a similar attenuation for the human host (1, 15). In the last-named patient (H.T.), tubercle bacilli recovered from the sputum at intervals during isoniazid therapy were studied from the point of view of isoniazid susceptibility and guinea pig virulence. At the fourth week of isoniazid therapy, tubercle bacilli from the sputum were both isoniazid-susceptible and virulent for guinea pigs. When isoniazid-resistant organisms emerged during therapy, a striking decrease in virulence was noted when these were inoculated into guinea pigs. Nevertheless, the patient's clinical condition did not parallel the change in guinea pig virulence, since several unfavorable clinical and roentgenographic changes were observed, leading to a pneumonectomy. From this case and others not included in this report, it is the opinion of the writers that the inability of tubercle bacilli to produce progressive tuberculosis in animals is not necessarily associated with a loss of ability to produce progressive tuberculosis in man.

DISCUSSION

The problem of the decrease in virulence of isoniazid-resistant tubercle bacilli has been one of the more recent challenges to the bacteriologist. Previous reports have dealt principally with bacilli obtained from sputum and with stock laboratory strains of *M. tuberculosis*. The present reports concern bacilli recovered directly from pulmonary tuberculous lesions resected from patients. The findings confirm, in general, those previously reported with respect to the correlation between isoniazid resistance and attenuation for the guinea pig both on direct inoculation of homogenates of resected pulmonary tissue and the guinea pig inoculation of cultures isolated from the resected tissue. Significant exceptions to this general correlation were noted, however, and require further study. Studies of catalase activity and of virulence with the intravenous inoculation route have not yet been carried out on this material.

The possibility has been suggested that conflicting reports on the correlation between isoniazid susceptibility and modified virulence for guinea pigs may be due to variations in technique. The possible chance for error in working with cultures containing mixtures of isoniazid-susceptible and isoniazid-resistant or-

ganisms, rather than with pure cultures of isoniazid-resistant organisms has been stressed (8, 11–13).

In the present study, variation in the degree of isoniazid susceptibility between the tubercle bacilli from one lesion and those from another in the same patient is quite evident, and the presence within single lesions of a mixed population in terms of isoniazid susceptibility can reasonably be postulated. However, in the present study, this was not reflected in increased virulence for guinea pigs, since virulence of organisms from all lesions but one was low. The virulence of "isoniazid-resistant" cultures may be explained by the presence of certain numbers of isoniazid-susceptible virulent organisms in the culture. The loss of virulence is less easy to explain on the same grounds, however, when obviously isoniazid-susceptible cultures or cultures of mixed isoniazid susceptibility are studied.

Steenken and Wolinsky (2) observed loss of virulence for guinea pigs in an H37Rv culture after it had been made resistant to PAS, streptomycin, neomycin, and viomycin by serial transfer in Tween®-albumin medium containing these respective drugs. The tubercle bacilli isolated from the 22 pulmonary lesions resected from the 8 patients in the present study were resistant to one or more drugs (streptomycin, PAS, isoniazid) in every instance. It is possible that resistance to these other drugs was a factor in the results of the present study.

SUMMARY

Tubercle bacilli isolated from 21 of 22 resected pulmonary lesions of 8 patients who received prolonged combined chemotherapy, including isoniazid, were attenuated for guinea pigs. The strains of tubercle bacilli, while resistant in some degree to isoniazid, in 14 cases showed variation in degree of *in vitro* susceptibility to streptomycin and PAS, as well as to isoniazid. In all instances, however, the strains obtained from the resected lesions were resistant to at least one of these three drugs. Four of 5 lesions from 2 patients yielded isoniazid-susceptible bacilli with slight or no virulence for guinea pigs.

The results suggest that, for undetermined reasons, isoniazid may alter the ability of tubercle bacilli to produce progressive tuberculosis in guinea pigs, but that the phenomenon is by no means unique to isoniazid-resistant bacilli.

The clinical and bacteriologic findings in one patient indicated that a decrease in the virulence of his bacilli for guinea pigs did not result in a similar attenuation of these microorganisms for the patient.

SUMARIO

Virulencia para los Cobayos de los Bacilos Tuberculosos Aislados de Lesiones Pulmonares Resecadas durante la Quimioterapia

Los bacilos tuberculosos aislados de veintiuna de veintidós lesiones pulmonares resecadas a 8 enfermos que recibieron prolongada quimioterapia combinada, incluso isoniacida, se mostraron atenuados para los cobayos. Aunque resistentes hasta cierto punto a la isoniacida, los microbios revelaron en 14 casos variación *in vitro* en la intensidad de su susceptibilidad a la estreptomicina, al ácido para-aminosalicílico (PAS) y a la isoniacida,

pero en todos los casos, fueron resistentes a lo menos a una de las drogas. Cuatro de cinco lesiones de 2 enfermos rindieron bacilos isoniacido-susceptibles dotados de virulencia leve o nula para los cobayos.

Estos resultados sugieren que, por alguna razón o razones indeterminadas, la isoniacida puede alterar la capacidad de los bacilos tuberculosos para producir tuberculosis evolutiva en los cobayos. Sin embargo, no es siempre necesaria la resistencia a la isoniacida para provocar este fenómeno.

Los hallazgos clínicos y bacteriológicos en un enfermo indicaron que una disminución de la virulencia de sus bacilos para los cobayos no dió por resultado una atenuación semejante de esos microbios para el enfermo mismo.

RESUME

Virulence des bacilles tuberculeux isolés à partir de lésions pulmonaires réséquées au cours de la chimiothérapie chez le cobaye

Des bacilles tuberculeux isolés à partir de vingt-et-une à vingt-deux pièces de résection pulmonaire chez 8 malades soumis à la chimiothérapie combinée prolongée, y compris l'isoniazide, ont présenté une virulence atténuée pour le cobaye. Les germes, bien que présentant un certain degré de résistance à l'isoniazide, dans 14 cas montraient des différences de degré de la sensibilité *in vitro* à la streptomycine, à l'acide para-aminosalicylique (PAS) et à l'isoniazide, mais dans tous les cas, ils se sont montrés résistants à l'une de ces drogues au moins. Quatre des cinq lésions prélevées chez deux patients renfermaient des bacilles isoniazides-sensibles n'ayant qu'une légère ou aucune virulence pour les cobayes.

Les résultats suggèrent que pour une ou plusieurs raisons indéterminées, l'isoniazide peut altérer la capacité des bacilles tuberculeux à produire une tuberculose évolutive chez le cobaye. Néanmoins, la résistance à l'isoniazide n'est pas toujours nécessaire pour provoquer ce phénomène.

Les résultats cliniques et bactériologiques observés chez un malade montraient qu'une réduction de la virulence de ses bacilles pour le cobaye ne coïncidait pas avec une même atténuation de la virulence des germes chez le malade lui-même.

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THE BEHAVIOR OF VARIOUS MYCOBACTERIA IN THE CHICK AND DUCK EMBRYO[1,2]

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INTRODUCTION

Early studies on the behavior of mycobacteria when inoculated onto the chorio-allantois of the chick embryo (1, 2) indicated that human and bovine tubercle bacilli produced similar lesions, but that bovine strains were slightly more virulent. Rather surprisingly, avian bacilli produced much less severe lesions.

Canat and Opie (3) gave detailed descriptions of the cytologic reactions in chick embryos inoculated with avian bacilli. Emmart and Smith (4) showed that the difference in the reaction produced by the virulent H37Rv and the avirulent H37Ra strains could be expressed quantitatively. Eggerth, Dresher, and McOsker (5) concluded that the chick embryo of six to eight days of age was more susceptible to infection with tubercle bacilli than older embryos. McNelly and Riddell (6) suggested that the chick embryo could be used with advantage in the routine isolation of tubercle bacilli. Lee and Stavitsky (7) described the development of lesions following the injection of relatively small amounts of a somewhat attenuated strain of human tubercle bacilli given intravenously. They suggested that the chick embryo could be used to test the activity of compounds against tubercle bacilli; Francis and Hoggarth (8) used the chick embryo for this purpose.

Moore (9) described the changes following inoculation of human, bovine, avian, fish, and snake tubercle bacilli, and of rat leprosy bacilli onto the chorio-allantois. The changes produced by human and avian tubercle bacilli were similar to those described by Costil and Bloch (2), but both Moore, and Emmart and Smith (10) concluded that bovine bacilli were less virulent for the chick embryo than human bacilli, and Moore concluded that the changes produced by bovine strains could readily be distinguished from those produced by human strains.

Both of these conclusions are at variance with the general conclusion that bovine bacilli are more virulent than human bacilli but that the cellular reactions produced by them are very similar (11, 12), and it will be seen that they are at variance with earlier findings in the chick embryo (1, 2). The purpose of the present study was to provide further data on this question and to confirm the rather surprising evidence that avian bacilli were less virulent for chick embryos than were mammalian bacilli. Observations are also presented on the behavior of other mycobacteria in chick and duck embryos.

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[2] Part of the work described in this paper was performed in the Biological Laboratories of Imperial Chemical Industries, Ltd., Manchester, England.

MATERIALS AND METHODS

Hen eggs incubated for ten to twelve days and duck eggs incubated for twelve to fourteen days were used. They were inoculated onto the chorio-allantois by the usual technique (13) and after a further seven days' incubation of hen eggs and ten to twelve days' incubation of duck eggs, the chorio-allantoic membranes were removed, after a few minutes' fixation with 10 per cent formol-saline, and the lesions were examined. The characteristics of the strains employed are shown below.

Human: Weybridge C, an old laboratory strain used for producing tuberculin at the Veterinary Laboratory, Weybridge, but shown to be fully virulent in numerous animal tests (12); "905," a fairly recently isolated virulent strain used by Martin (14) for chemotherapeutic tests in mice; and "7890," a fully virulent recently isolated strain.

"Lister 48," an old strain obtained from the British National Collection of Type Cultures. It failed to produce progressive disease in guinea pigs even after intraperitoneal injection of 5 mg. of culture.

Bovine: "A.N.5," an old laboratory strain obtained from the Veterinary Laboratory, Weybridge, and shown to be fully virulent in numerous animal tests (12). Bovine "eye" and "mesenteric node" were fully virulent, recently isolated strains, obtained from the eye and a mesenteric node of bovines.

"Lister 46," an old strain obtained from the British National Collection of Type Cultures. It failed to produce progressive disease in guinea pigs even after the intraperitoneal injection of 5 mg. of culture.

Mycobacterium tuberculosis var. *muris* Brooke: Two strains of the vole bacillus (15) were obtained from Dr. J. A. Young of Cambridge. Strain G564 was known to be more virulent for animals than strain LV285 (16) and it produced progressive disease in mice, rabbits, and guinea pigs (12).

Avian: "S.H.1": This strain was recently isolated from the enlarged spleen of a fowl with generalized tuberculosis. It had the cultural characteristics of an avian strain, and doses of 10^{-1} to 10^{-2} mg. given intravenously killed 6 young chickens after periods of one to two months. It was also fully virulent for rabbits. Strain "6730," an old avirulent laboratory strain obtained from the Veterinary Laboratory, Weybridge (12).

RESULTS

Macroscopic Changes Produced by Inoculation onto the Chorio-Allantois

Duck eggs inoculated with 2 mg. of virulent human or bovine tubercle bacilli showed extensive nodular lesions. There was no difference in the lesions produced by the one old laboratory strain and two recently isolated strains of each type of mammalian bacilli, all of which were virulent. Membranes inoculated with 0.2 mg. generally developed less severe lesions (figures 1, 2, and 3), but individual membranes could not be differentiated with certainty from those inoculated with 2 mg. Membranes inoculated with 0.02 mg. sometimes developed quite large lesions, but they were usually small. Inoculation of similar doses onto hen eggs usually produced slightly less severe lesions (figures 4 and 5).

The two avirulent strains, L.46 (bovine) and L.48 (human), produced much less severe lesions, but even with these strains doses of 0.2 mg. produced definite lesions.

Vole bacilli, strain G546, produced similar lesions to avirulent human and bovine strains, and vole bacilli, strain LV285, slightly less severe lesions.

Virulent avian tubercle bacilli were not inoculated on duck embryos, but on chick embryos they produced even less reaction than avirulent human or bovine

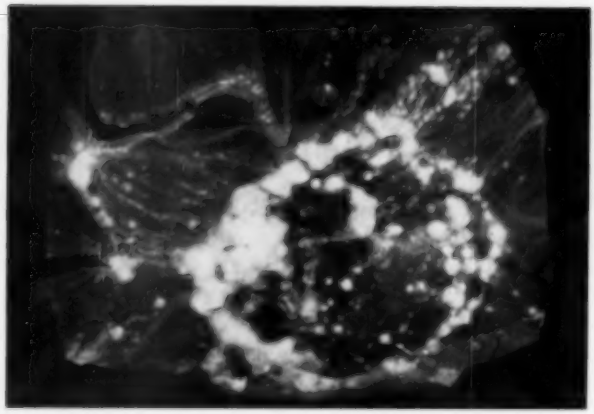

FIG. 1. Chorio-allantois, duck embryo 290: 0.2 mg. of bovine tubercle bacilli (A.N.5). Large nodular lesions.

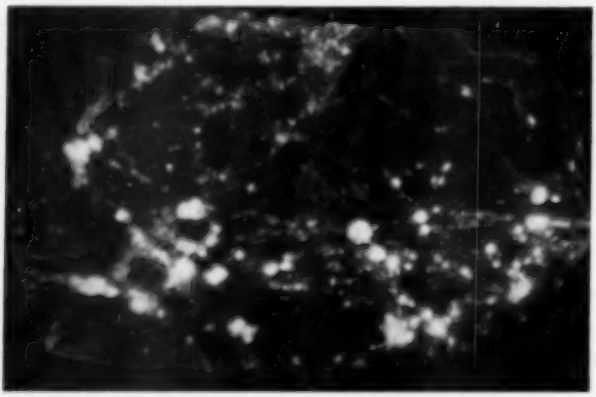

FIG. 2. Chorio-allantois, duck embryo 288: 0.2 mg. of bovine tubercle bacilli (A.N.5). Large and small nodular lesions.

bacilli, i.e., hardly any nodular lesions at all (figure 6). An avirulent strain (6730) produced virtually no lesions.

Histologic Changes Produced by Inoculation onto the Chorio-Allantois

In duck embryos the virulent human and bovine strains grew freely on the epithelium and in the mesoderm, so that there were enormous numbers present six to ten days after inoculation (figure 7), and they were often arranged in "cordlike" masses (*see* figure 10). Epithelioid cells developed, but by twelve days they were very eosinophilic and vacuolated, and there were often considerable areas of necrosis (figure 9), sometimes with complete breakdown of the

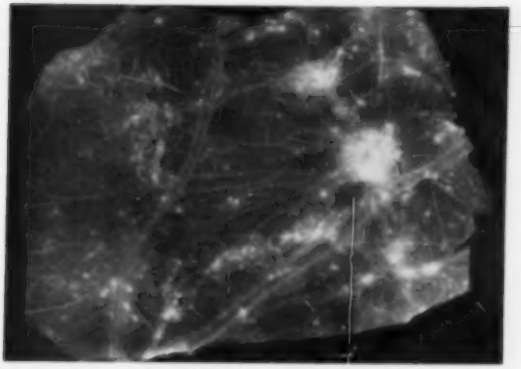

FIG. 3. Chorio-allantois, duck embryo 387: 0.2 mg. of human tubercle bacilli (905). Lesions less severe than in figures 1 and 2.

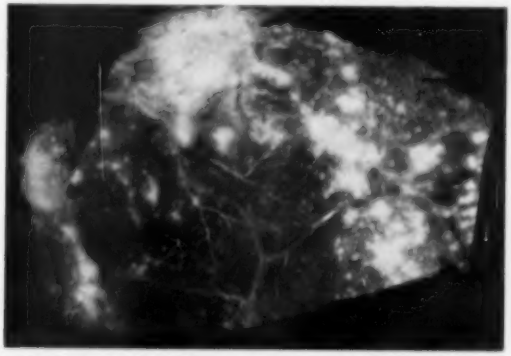

FIG. 4. Chorio-allantois, chick embryo 304: 2 mg. of bovine bacilli (mesenteric node). With the larger dose lesions more severe than in figures 1 and 2.

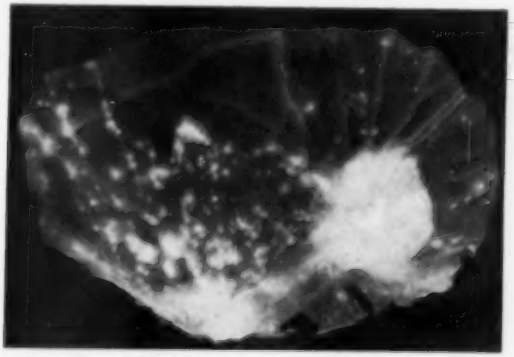

FIG. 5. Chorio-allantois, chick embryo 331: 2 mg. of human tubercle bacilli (7890). The two largest nodular lesions may be partly due to trauma.

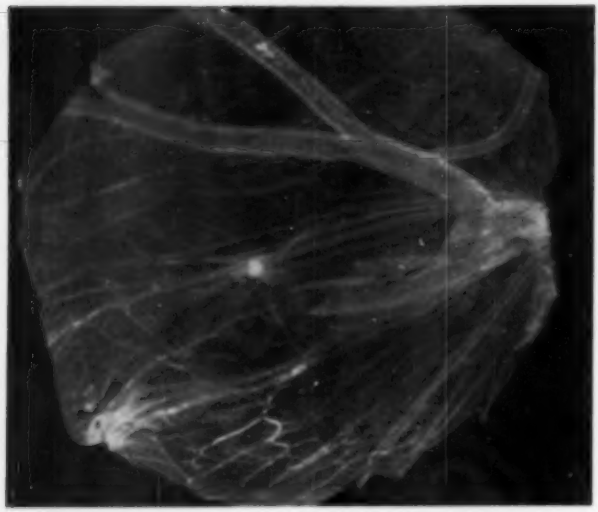

FIG. 6. Chorio-allantois, chick embryo 356: 2 mg. of avian tubercle bacilli (S.H.1). Only very faint lesions.

overlying epithelium. Some fibrosis and irregular giant-cell formation were observed. Large invaginations of the epithelium and "pearls" containing numerous bacilli (figures 7, 8, and 9) were common in membranes inoculated with bovine bacilli and they occurred, but were much less numerous, in membranes inoculated with human bacilli. Eosinophilic polymorphonuclear cells were numerous in membranes inoculated with either type, except in the areas of most intense mononuclear reaction, but they were usually more numerous with the human type. In general, the impression gained was that bovine bacilli were slightly more virulent and produced slightly more necrosis than human bacilli.

In chick embryos the lesions were similar, and irregular giant cells, sometimes containing a mass of bacilli (figure 11) and a tubercle (figure 12), somewhat resembling those seen in the adult fowl infected with avian bacilli (17), were seen. Large numbers of bacilli were sometimes seen in the mesoderm (figure 10) but they were usually less numerous than in duck embryos, and invagination of the epithelium and "pearls" were much less common. With other mycobacteria only slight differences were observed between the reactions in duck and chick embryos.

The almost completely avirulent strains L.46 (bovine) and L.48 (human) were examined histologically only in the chick embryo. Strain L.48 multiplied on the surface of the chorio-allantois, but very few bacilli were found in the mesoderm; when they did occur there was the usual reaction of epithelioid cells, but only a few eosinophils. The avirulent bovine strain, L.46, had definitely greater powers of multiplication in the mesoderm, fairly numerous groups being readily seen under the two-thirds objective. There were typical groups of epi-

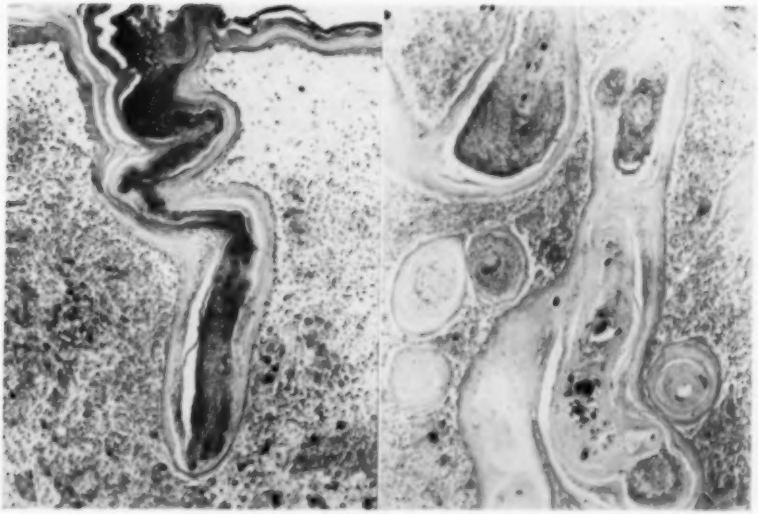

FIG. 7 (Left). Chorio-allantois, duck embryo 157: 2 mg. of bovine tubercle bacilli (A.N.5). Dark acid-fast bacilli can be seen on the surface of the keratinized chorio-allantois, lying among necrotic cells in the epithelial invagination, and in the mesoderm. (acid-fast stain, ×80)

FIG. 8 (Right). Chorio-allantois, duck embryo 157: 2 mg. of bovine tubercle bacilli (A.N.5). Complex invaginations of the epithelium containing groups of black tubercle bacilli. Some invaginations are cut in cross section and give the appearance of "pearls." (acid-fast stain, ×80)

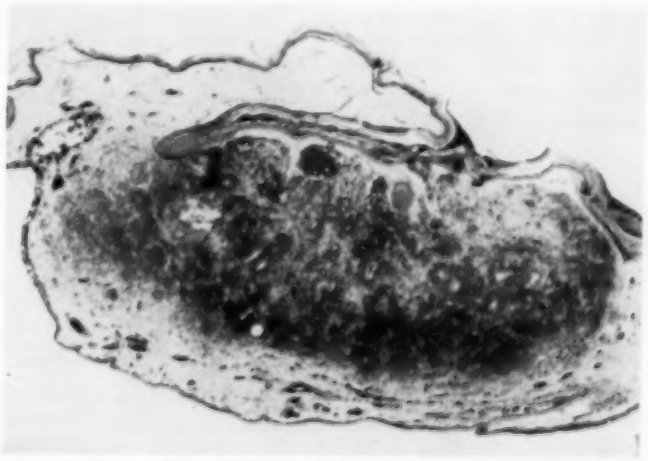

FIG. 9. Chorio-allantois, duck embryo 153: 2 mg. of bovine tubercle bacilli (A.N.5). A large necrotic tubercle below the normal level of the endoderm. A large invagination contains blood corpuscles, inflammatory cells, and tubercle bacilli. (H and E stain, ×26)

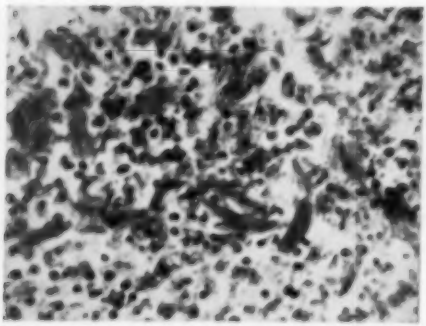

FIG. 10. Chorio-allantois, chick embryo 528: 2 mg. of bovine tubercle bacilli (A.N.5). Beaded tubercle bacilli arranged in cordlike masses in the mesoderm; some cells are necrotic, and the overlying epithelium had disappeared. (acid-fast stain, ×670)

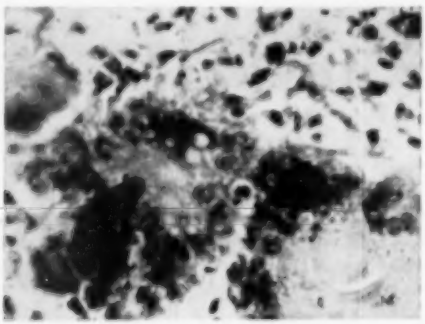

FIG. 11. Chorio-allantois, chick embryo 518: 2 mg. of human tubercle bacilli (Weybridge C). Irregular giant cells, one of which contains a large clump of bacilli. There are smaller groups in the giant cells and in the mesodermal cells, but cells do not become stuffed with bacilli as in avian infection.

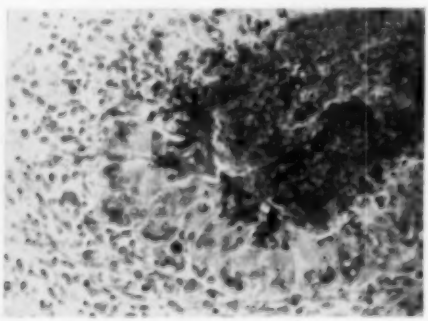

FIG. 12. Chorio-allantois, chick embryo 528: 2 mg. of bovine tubercle bacilli (A.N.5). An area of necrotic cells, containing few bacilli, surrounded by elongated epithelioid cells. This appearance resembles that sometimes seen in the adult fowl infected with avian bacilli (17, p. 145). (H and E stain, ×300)

thelioid cells, a few irregular giant cells, some fibroblasts, and a few "pearls," but few eosinophils.

The virulent vole bacillus (strain G564) multiplied freely on the surface of the epithelium and produced many more lesions in the mesoderm than avirulent mammalian tubercle bacilli, but much fewer than virulent mammalian strains. Within any one lesion in duck or chick embryos, bacilli were almost as numerous as with virulent mammalian strains, but they were largely intracellular. Epithelioid cells, some irregular giant cells, quite numerous "pearls," numerous eosinophilic cells, and fibroblasts were all observed and there were well-defined areas of necrosis. The avirulent strain, LV285, produced less severe lesions.

The virulent avian strain, S.H.1, multiplied readily on the surface of the epithelium, but the large masses of bacteria in necrotic mesoderm, with breakdown of epithelium, observed with virulent mammalian strains were not seen. There were small numbers of lesions in the mesoderm which consisted of epithelioid cells, the cytoplasm of which was stuffed with bacilli (figure 13); there were a few extracellular bacilli. In sections stained by hematoxylin and eosin, cells containing bacilli appeared as rather large, somewhat basophilic, epithelioid cells, but there was little other cellular reaction. Thus virulent avian bacilli provoked less reaction than avirulent mammalian bacilli. The avirulent avian strain multiplied on the surface of the epithelium, but only occasionally invaded the mesoderm and then produced very slight changes.

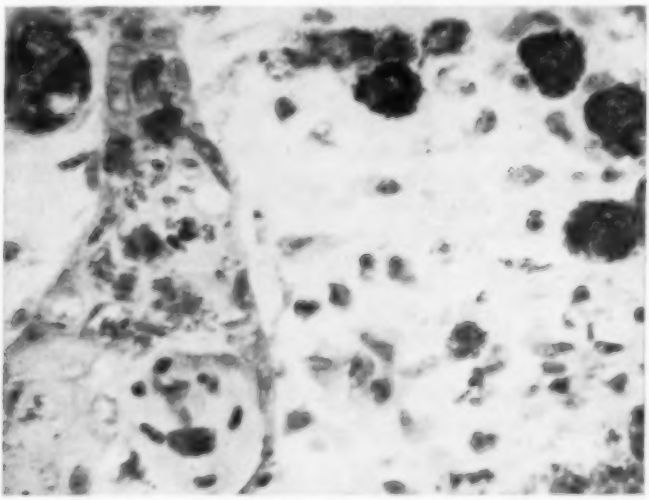

FIG. 13. Chorio-allantois, chick embryo 533: 2 mg. of avian tubercle bacilli (S.H.1). Clumps of bacilli in a syncitial cell group on left and epithelioid cells stuffed with bacilli on right. In most areas bacilli are more numerous on the surface of the chorio-allantois than in the mesoderm. (acid-fast stain, ×670)

TABLE 1

SURVIVAL TIME (DAYS) OF CHICK-EMBRYOS INFECTED INTRAVENOUSLY WITH 1.5 MG. OF VIRULENT TUBERCLE BACILLI

Strain	Number of Embryos Surviving One Day	Embryos Dead on Day:										Average Survival Time
		2	3	4	5	6	7	8	9	10	11	
Avian (S.H.1)	26	5	4	0	0	4	0	1	5	5	2	6.6
Bovine (A.N.5)	30	11	5	2	5	6	0	1				3.8

Intravenous Infection of Embryos

The apparent lower virulence of avian than mammalian strains for the chick embryo when inoculated onto the chorio-allantois was surprising. Consequently, a series of experiments was carried out in which virulent avian or bovine tubercle bacilli were injected intravenously into twelve-day-old chick embryos, and the results are shown in table 1. The virulence of the avian strain for rabbits was confirmed at the same time.

Equal numbers of embryos were inoculated with avian and bovine bacilli and they were incubated together, so there can be little doubt that the bovine bacilli were the more virulent. This is still true even if one excludes the embryos which died on the second day. Histologic examination of the embryos showed that, despite this, avian bacilli multiplied much more freely than bovine bacilli. In embryos killed or dying within three days of inoculation with avian bacilli, very few organisms and no clumps were observed. No embryos died on the fourth or fifth days and none was killed.

There was little difference between embryos which died or were killed six to fourteen days after inoculation except that, in those which died early, the bacilli in the liver were usually not in such dense intracellular clumps as those which died later, and a general description will suffice. Embryos dying or killed more than nine days after inoculation had, of course, hatched. As already stated, nearly every embryo had numerous dense clumps of tubercle bacilli in the liver and spleen, contained in groups of epithelioid cells. There were occasional groups of bacilli in the interstitial tissue of the lung and in the pulmonary epithelium. There were often masses of bacilli in the glomeruli of the kidney (figure 14) and a few in the interstitial tissue. There were dense groups of bacilli in the mesoderm of the chorio-allantoic membrane and of the yolk-sac of most embryos, and masses of bacilli on the surface of the chorio-allantois were also quite frequent. Groups of bacilli were seen in the meninges, brain sulci, and brain substance of several embryos.

Most of the embryos infected with bovine bacilli died early, and only occasional groups of bacilli were seen in embryos which died on the fourth and fifth days after inoculation. Four embryos which died on the sixth day all contained many fewer organisms than most of the embryos infected with avian bacilli. Bacilli were observed in the mesoderm of the chorio-allantois, but not on the surface.

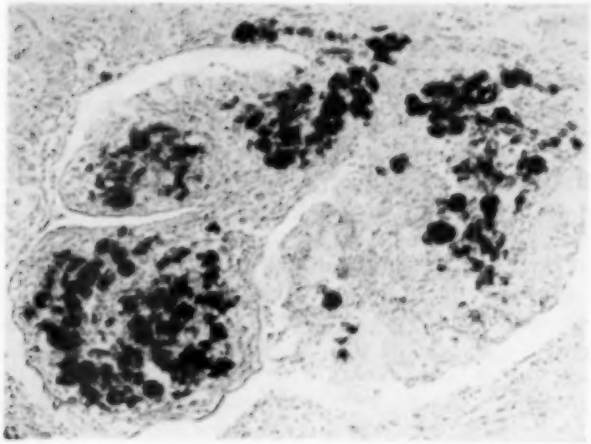

FIG. 14. Kidney, chick embryo 456: 2 mg. of avian tubercle bacilli (8.H.1) intravenously. Masses of bacilli in glomeruli and in surrounding kidney tissue. (acid-fast stain, ×150)

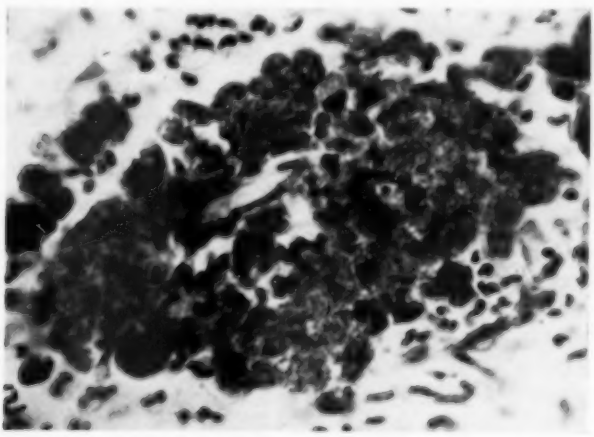

FIG. 15. Chorio-allantois, chick embryo 508: Suspension of rat leprosy bacilli. Cells surrounding a small vessel in the mesoderm are stuffed with acid-fast bacilli as in avian-type infection. Leprosy bacilli do not, however, multiply. (acid-fast stain, ×670)

Rat Leprosy Bacilli

Chick embryos were inoculated onto the chorio-allantois with a heavy suspension of rat leprosy bacilli. The macroscopic and microscopic appearances of the chorio-allantois were similar to those seen following infection with avian tubercle bacilli, and cells stuffed with acid-fast bacilli (figure 15) gave a very characteristic appearance. However, estimations of the numbers of bacilli pres-

ent (8) failed to provide any indication of multiplication, and the organisms disappeared after three to four passages in chick embryos.

DISCUSSION

The findings with human tubercle bacilli were similar to those of other workers, and the conclusion of Moore (9) and Emmart and Smith (4, 10) that mammalian strains of tubercle bacilli were placed in approximately the same order of virulence by the reaction they produced in the chorio-allantoic membrane was confirmed and extended. Thus it was shown, particularly on histologic examination, that virulent strains of avian bacilli or of the vole bacillus produced greater lesions than avirulent strains of the respective organisms. Virulent vole bacilli produced a greater reaction than avirulent mammalian tubercle bacilli or virulent avian bacilli.

The conclusion that bovine bacilli were slightly more virulent than human (1, 2) was confirmed, but the differences between the reactions produced by human and bovine bacilli were only those of degree and did not serve to differentiate between the types. These results are therefore in accord with observations in animals (11, 12).

Histologic observations and the mortality following intravenous infection confirmed the earlier reports (2, 9) that avian bacilli were less virulent for the chick embryo than mammalian bacilli. It will be seen, therefore, that the cells of the chick embryo behaved like those of tissue cultures (18–20) and of mice (12). Thus avian bacilli appeared to have very little toxicity for cells of the chick embryo, and a characteristic picture of cells stuffed with acid-fast bacilli was produced. Mammalian bacilli were considerably more toxic and cells were destroyed at an early stage, so that corded masses of bacilli were seen lying free in necrotic tissue. Bovine bacilli appeared to be slightly more toxic than human bacilli, and embryos which died following intravenous infectioe with bovine bacilli had many fewer bacteria in their organs than similar embryos infected with avian bacilli. Even avirulent mammalian and vole bacilli produced a greater reaction than virulent avian bacilli on the chorio-allantois, and Moore (9) found that acid-fast bacilli isolated from fish and snakes provoked a vigorous reaction. Vole bacilli, but not avirulent mammalian bacilli, produced the characteristic picture of cells stuffed with bacilli.

The fact that rat leprosy bacilli did not multiply on the chorio-allantois was in accord with the findings of Stavitsky and Beck (21), who found that strains of *M. johnei* requiring the johnei growth factor ("mycobactin" (22)) do not grow on the chorio-allantois, but strains that do not require mycobactin multiply quite readily.

The purpose of the present study was to compare the behavior of various mycobacteria in the cells of the chick embryo, which has not developed species-specific resistance. It will be seen that under these conditions the various types of tubercle bacilli have about the same relative virulence and toxicity as they do in the cells of tissue culture derived from a variety of species (18–20). The hatched bird acquires the power of preventing the multiplication of mammalian bacilli, and consequently the latter are unable to exert their toxic effects and

do not produce progressive disease or lesions. It may seem strange that the relative pathogenicity of avian and mammalian tubercle bacilli is different in the embryo and the hatched bird, but it appears that the response of fetal tissue in the guinea pig may be different from that in the adult (23, 24).

SUMMARY

Human, bovine, and avian types of tubercle bacilli, vole acid-fast bacilli, and rat leprosy bacilli were inoculated onto the chorio-allantois of chick embryos. Most strains were inoculated onto the chorio-allantois of the duck embryo, and two were inoculated intravenously into chick embryos.

Virulent mammalian strains produced pocklike lesions on the chorio-allantois and a vigorous cellular reaction. Bovine bacilli multiplied more freely than human bacilli in duck embryos and produced greater invaginations of the epithelium and more "pearls" than human strains. In chick embryos these latter changes were approximately the same with both types of bacilli and were less severe than in duck embryos. Contrary to some previous observations, bovine bacilli were slightly more virulent than human bacilli and it was not possible to distinguish between the lesions produced by these two types.

It was confirmed that differences of virulence within one type of tubercle bacilli could be detected. Avirulent mammalian bacilli produced much smaller macroscopic lesions than virulent strains and had much less power of invading the mesoderm.

Virulent avian bacilli produced much smaller macroscopic lesions than mammalian bacilli. They multiplied freely on the surface of the chorio-allantois, but did not invade the mesoderm so actively as virulent mammalian strains. The cytoplasm of epithelioid cells became stuffed with avian bacilli, but they produced very little necrosis and less cellular reaction than avirulent mammalian strains.

When given intravenously, avian bacilli were less pathogenic to chick embryos than bovine bacilli despite the fact that they multiplied more, thus confirming that they were less toxic. Following intravenous infection, great numbers of avian bacilli were found in the kidneys, liver, chorio-allantois, and yolk sac. Smaller numbers were found in all other organs, including the brain.

Virulent vole acid-fast bacilli produced similar macroscopic changes to avirulent mammalian bacilli and greater changes than virulent avian bacilli. They produced more severe histologic changes than avirulent mammalian bacilli or avian bacilli, and, as with avian bacilli, the cytoplasm of epithelioid cells became stuffed with vole bacilli.

Inoculation of the chorio-allantois with large numbers of rat leprosy bacilli produced a picture similar to that following inoculation with avian bacilli, but it was shown that the bacilli did not multiply.

SUMARIO

Comportamiento de Varias Micobacterias en los Embriones de Pollo y de Pato

En la membrana corio-alantoides de embriones de pollo, inoculáronse bacilos tuberculosos de tipos humano, bovino y aviario, bacilos ácidorresistentes de ratón campesino

(microto) y bacilos de lepra murina. La mayor parte de las cepas fueron también inoculadas en la corio-alantoides del embrión de pato y dos fueron inoculadas intravenosamente en embriones de pollo.

Cepas virulentas de mamífero produjeron lesiones varioloideas en la corio-alantoides y una enérgica reacción celular. Los bacilos bovinos se multiplicaron más que los humanos en los embriones de pato y produjeron mayores invaginaciones del epitelio y más "perlas" que los últimos. En los embriones de pollo, estas últimas alteraciones fueron aproximadamente idénticas con ambas formas de bacilos y menos graves que en los embriones de pato. En contraposición a algunas observaciones anteriores, los bacilos bovinos se mostraron poco más virulentos que los humanos, sin que fuera posible distinguir las lesiones producidas por uno u otro tipo.

Confírmose que podían descubrirse diferencias de la virulencia dentro de un tipo de bacilos tuberculosos. Los bacilos avirulentos de mamífero produjeron lesiones macroscópicas mucho más pequeñas que las cepas virulentas y poseían una capacidad mucho menor para invadir el mesodermo.

Los bacilos aviarios virulentos produjeron lesiones macroscópicas mucho más pequeñas que los de mamífero. Se multiplicaron abundantemente en la superficie de la corio-alantoides, pero no invadieron el mesodermo tan activamente como las cepas virulentas de mamífero. El citoplasma de las células epitelioideas se atestó de bacilos aviarios, pero éstos produjeron muy poco esfacelo y menos reacción celular que las cepas avirulentas de mamífero.

Administrados endovenosamente, los bacilos aviarios se mostraron menos patógenos que los bovinos para los embriones de pollo, a pesar de multiplicarse más, confirmando así que eran menos tóxicos. Después de la inyección intravenosa, se encontraron grandes cantidades de bacilos aviarios en los riñones, el hígado, la corio-alantoides y el ovisaco. Se encontraron menores cantidades en todos los demás órganos, incluso el cerebro.

Los bacilos ácidorresistentes virulentos de microto produjeron lesiones macroscópicas semejantes a las de los bacilos avirulentos de mamífero y mayores alteraciones que los bacilos aviarios virulentos. Produjeron alteraciones histológicas más graves que los bacilos avirulentos de mamífero o los aviarios y, lo mismo que con los últimos, se atestó de bacilos de microto el citoplasma de las células epitelioideas.

La inoculación de la corio-alantoides con grandes cantidades de bacilos de lepra murina produjo un cuadro semejante al consecutivo a la inoculación de bacilos aviarios, pero se demostró que los bacilos no se multiplicaban.

RESUME

Comportement de diverses mycobactéries dans l'embryon du poulet et du canard

Des bacilles tuberculeux du type humain, bovin et aviaire, des bacilles acido-résistants de rongeur et le *M. leprae murium* ont été inoculés dans la membrane chorio-allantoïdienne de l'embryon de poulet. La plupart des souches étaient inoculées dans la chorio-allantoïde du canard, deux furent inoculées par voie veineuse dans l'embryon de poulet.

Les souches bovines virulentes produisaient des lésions pustuleuses sur la chorio-allantoïde et une forte réaction cellulaire. Les bacilles bovins se reproduisaient plus facilement que les bacilles humains chez l'embryon de canard et déterminait une invagination de l'épithélium plus marquée et plus de "perles" que les souches humaines. Dans l'embryon de poulet ces manifestations étaient sensiblement les mêmes pour les deux types de bacilles et elles étaient moins accentuées qu'avec l'embryon de canard. A l'encontre de certaines observations antérieures, les bacilles bovins étaient légèrement plus virulents que les bacilles humains et il n'était pas possible d'établir une distinction entre les lésions produites par l'un ou l'autre de ces deux types.

La confirmation de différences de virulence pour un même type de bacilles tuberculeux a pu être obtenue. Les bacilles bovins non virulents provoquaient des lésions histologiques beaucoup plus réduites que celles des souches virulentes et leur pouvoir d'invasion du mésoderme était beaucoup moins marqué.

Les bacilles aviaires virulents produisaient des lésions macroscopiques plus réduites que les bacilles bovins. Ils se reproduisaient facilement à la surface de la chorio-allantoïde, mais n'envahissaient pas le mésoderme avec la même activité que les souches bovines virulentes. Le cytoplasme des cellules épithélioïdes était bourré de bacilles aviaires, mais la nécrose et la réaction cellulaire étaient moins marquées que lorsqu'il s'agissait de souches bovines avirulentes.

Les bacilles aviaires inoculés par voie veineuse étaient moins pathogènes pour l'embryon de poulet que les bacilles bovins, en dépit d'une reproduction plus intense, ce qui confirmait leur toxicité plus faible. A la suite de l'infection intraveineuse on découvrait un grand nombre de bacilles aviaires dans les reins, le foie et dans les membranes chorio-allantoïdienne et vitelline. Dans les autres organes, y compris le cerveau, leur nombre était plus réduit.

Les bacilles acido-résistants de rongeurs produisaient des altérations macroscopiques analogues à celles des bacilles bovins avirulents et des altérations plus marquées que les bacilles bovins ou aviaires virulents. Ils produisaient des modifications histologiques plus marquées que les bacilles bovins ou aviaires avirulents et, de même que les bacilles aviaires, le cytoplasme des cellules épithélioïdes était bourré de bacilles de rongeurs.

L'inoculation de la chorio-allantoïde avec le *M. lepræ murium*, en grand nombre, déterminait le même aspect que celui observé après l'inoculation des bacilles aviaires, mais il a été démontré que ces bacilles ne se reproduisaient pas.

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Editorial

The Place of the Laboratory in the Tuberculosis Sanatorium[1]

The place of the laboratory in the sanatorium has been discussed many times since it emerged from the small out-house in which it operated virtually without equipment or skill. In such laboratories in tuberculosis sanatoriums the examination of one sputum smear obtained on admission to the hospital, and, often, one at discharge constituted the patient's total relationship with that unit of the institution. The tests were performed by a patient or an ex-patient to whom the doctor had given one or two brief demonstrations. The growth from this meager beginning to the modern sanatorium laboratory represents a fundamental change in attitude which has grown out of the demonstrated services such a unit may render.

It is obvious that the functions of the laboratory and the type of work requested will vary widely, depending upon many factors, such as the interests of the clinician, the condition of the patient, and the capacity and range of activity of the laboratory personnel. In general, these functions may be thought of under several broad headings.

The first of these is the *service* function. It is trite to state that the prime purpose of the laboratory and its personnel is to stand as a service unit to the clinician to carry through on any test, study, or problem which will aid the physician in his care of the patient. The laboratory should be equipped, and its staff prepared, to make any test or determination likely to be requested of any well-ordered laboratory in any first-rate hospital. It should report only the result and not attempt its interpretation.

Laboratory directors, laboratory personnel, and most clinicians deplore the practice, all too often used by some, of submitting requests for "baker's dozen" tests as a "screen"—many of them illogically related to the case. Such methods sometimes lead to the correct diagnosis, but surely the astute clinician will wish to evaluate his patient clinically and then request those laboratory studies which he deems germane to the situation. Subsequently, as the circumstances indicate, additional procedures may be requested. This procedure is far better than the use of what might be called the "blind plunge" method from the very beginning. The laboratory, to be successful, must be practical (not advisory), "down to earth," and without decoration or tinsel. It is always to be remembered that helpful service to the clinician and, through him, to the patient must be the basic aim underlying the operation of the laboratory.

It is possible to carry out an unlimited number of tests and examinations in the laboratory, some of which at least are in the nature of "window dressing." Whatever the range *could* be, the laboratory must be able to make practical evaluation of bacteriologic, chemical (including urinalysis), hematologic, and tissue specimens as the need arises.

[1] Presented in part at the meeting of the California Tuberculosis and Health Association and the California Trudeau Society, San Francisco, April 2, 1954.

All of these are important, but it is clear that the detection of tubercle bacilli means too much in the diagnosis and treatment of the tuberculous patient to allow less than repeated, prolonged, conscientious search of properly selected, prepared, and stained material. What is true for diagnosis holds with equal force during the active period of treatment when the reappearance of tubercle bacilli in the sputum may presage retrogression as the patient begins to increase his exercise, or during convalescence after thoracoplasty or resection, or especially for the weeks following closely upon discontinuation of chemotherapy.

A bacteriologic item of increasing importance next to the detection of bacilli has come to be the determination whether those bacilli detected are living, and this stands as a challenge to all of us today in this field. Work is underway at present to further elucidate this question of the death and resurrection of the tubercle bacillus.

The second broad heading, with respect to the role of the laboratory, is its range of service. The changing picture in the sanatorium reflects itself in the laboratory and calls for adjustment and, at times, expansion of services. Twenty-five years ago, for instance, of 100 patients with chronic disease of the chest, a diagnosis of tuberculosis would have been the correct one in approximately 90 instances. Today, tuberculosis would be present in only 50 or 60 of 100 such patients.

The implications of this change in the capacity and aims of the laboratory are obvious because they bring the need for meeting added clinical problems in differential diagnosis, and thus added preparation and readiness in the laboratory to meet requested tests and determinations in a wider range of diseases. This calls for an additional amount of good bacteriologic work and often for additional experience in the evaluation of body fluids or biopsy tissue from parts of the body not usually brought to account by tuberculosis.

Such diseases as coccidioidomycosis, histoplasmosis, blastomycosis, cryptococcal and other, rarer fungal infections stand among those encountered frequently as problems for elimination in differential diagnosis. Naturally, the laboratory personnel must keep abreast of the best practical approaches in such areas, and should have the imagination and ingenuity to apply proper procedures when they are indicated. These people must be alert to the unsuspected in diagnosis and ready to recognize signs of possible significance in the examination, whether or not the request for the test pointed to the likely presence of such signs.

The average age of our tuberculous patients is higher today. In these patients, time and circumstance have added strains and insults. They introduce additional challenge to the laboratory, for the wear and tear of time has often produced limitation upon the patient's respiratory physiology. In such patients, functional evaluation of the lungs as a part of the total "work-up" is called for. Again, the efficient laboratory will be prepared by equipment and "know how" to take such requirements in stride, for, after all, its function is to provide the clinician with whatever information may be available in the situation.

The increasingly prominent place of the surgeon in the clinical management of tuberculosis leads almost automatically to a heightened concern in the laboratory staff for histologic as well as bacteriologic study of resected tissue. This means a

reawakening of interest in the anatomic and pathologic phenomena associated with health and disease.

A third broad heading concerning the laboratory has to do with protection of personnel. It is recognized that the laboratory is the most highly contaminated area in the hospital and that it should have the utmost in personnel protection. The laboratory director should be the person to whom those in other areas of the hospital look for guidance. He must be familiar with the "risk areas"—danger spots and moments—and should, by use of ventilation, hoods, ultraviolet lights, and other proper protective techniques, at indicated times and locations provide the requisite safety factors. Increasing fear can be discounted in employment anywhere in the sanatorium if such techniques are recognized and used. One needs but to employ these available precautions to dispel all fear.

The final broad heading of this subject is the question of laboratory research. "Shop talk" around the lunch table brings out the fact that almost every day some patient presents problems and questions which puzzle the clinician at the bedside and concerning which he would appreciate more knowledge. This occurs, obviously, because there remain in medicine many unanswered questions. In those institutions where efforts are being made to answer some of these persisting questions, it frequently turns out that the laboratory is a sort of "hide out" to which the clinician may go for discussion. In such a retreat, which might be dubbed the "gas house," he finds time to talk with a congenial spirit or two.

These are elements that contribute ideas which need exploration and, often, techniques of approach and the enthusiasm to carry on. Exchange of ideas that grow out of experience and observation at the bedside or that come from reading or reflection leads one often to the eventual solution of numerous problems and represents one maneuver by which a good many research problems are started and carried on their way.

A review of the progress made in the treatment of tuberculosis and in the flow of added knowledge of the nature of the disease reveals the prominent portion that has been derived from the laboratory. Koch's discovery of the tubercle bacillus and of tuberculin, and the vast amount of subsequent study of that microorganism and its components, the basic work on the phenomena of immunity and of protection, prolonged and effective studies in chemotherapy and the experimental application of these drugs—these are but a few examples to indicate the range of effort put forth in the laboratory for the betterment of the tuberculous patient. And they have set the pace for continuing laboratory effort to this end. One needs but to refer to the current inspiring list of projects now sponsored by the Committee on Medical Research of the American Trudeau Society, Medical Section of the National Tuberculosis Association, to realize with what telling effect the sanatorium laboratory is carrying on original research. The still unsolved problems are legion and the challenge great. Through investigation the laboratory can be a dynamic unit at the heart of the over-all sanatorium effort.

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Notes

PHASE CONTRAST STUDIES OF CHANGES PRODUCED IN THE CYTOLOGY OF TUBERCLE BACILLI DURING GROWTH

A thin suspension prepared from a one-month-old culture of tubercle bacilli (BCG strain) grown on Löwenstein-Jensen medium was inoculated on Löwenstein-Jensen plates. The culture was incubated for one month at 37°C. and impression smears were made daily on cover slips which were washed thoroughly in water, dried, and examined

FIG. 1. One-month-old culture of tubercle bacilli. The bacilli are short and dense. There is no differentiation of the internal structure. (×1,500)

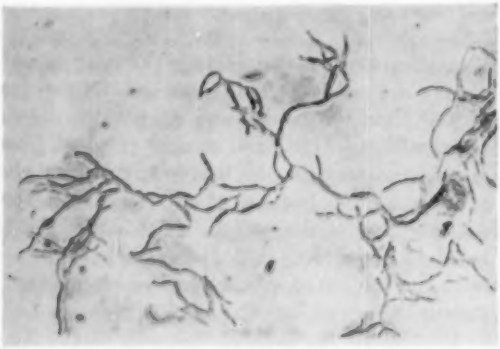

FIG. 2. Filamentous forms of the bacilli seen after three days. (×1,500)

under the phase contrast microscope. Similar studies were made by W. Roth (Schweiz. f. Path. u. Bakt., 1949, *12*, 451).

As may be seen in figures 1 to 4, inclusive, the one-month-old bacilli used for inoculation were short and dense, and no differentiation of the internal structure could be made out (figure 1). After three days, the filamentous forms of the bacilli were seen. These

FIG. 3

FIG. 4

FIGS. 3 and 4. After seven days the filamentous form breaks up into small rods. The cytoplasmic granules can be clearly seen. (×1,500)

bacilli were less dense but without structural clarity (figure 2). The same forms were seen up to the seventh day. After seven days, these long bacilli divided into small rods, in which there was a clear differentiation of the cytoplasm and cytoplasmic granules (figure 3). After three weeks the bacilli again started to lose their structural clarity.

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ELECTRONMICROSCOPIC AND PHASE CONTRAST STUDIES OF EFFECTS OF PARA-AMINOSALICYLIC ACID, ISONIAZID, AND VIOMYCIN ON TUBERCLE BACILLI

In a previous communication (Am. Rev. Tuberc., 1954, *70*, 328) the writers reported on the effect of streptomycin on the cytology of tubercle bacilli. It was observed that streptomycin caused elongation and swelling of the bacilli, followed by disintegration of the cytoplasm. The present report is concerned with the effect of para-aminosalicylic acid (PAS), isoniazid, and viomycin on the cytology of tubercle bacilli.

The procedure for electronmicroscopic studies was the same as was adopted by the writers for studies on the action of streptomycin. For phase contrast microscopy, smears on slides were fixed over osmic acid vapors and examined.

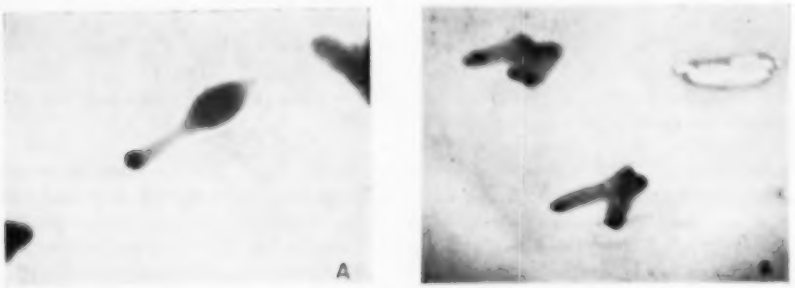

FIG. 1 *A*. An elongated bacillus examined after seventy-two hours of treatment with PAS, showing bulging of the mitochondria at one end. For comparison with untreated tubercle bacilli, see *B*. (×21,000)

B. Normal appearance of untreated tubercle bacilli under electron microscope; from a four-day-old culture of bovine tubercle bacilli showing mitochondria and vacuoles. (×21,000)

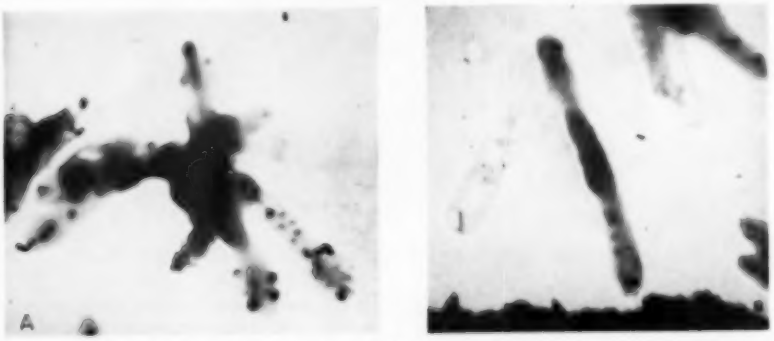

FIG. 2 *A* and *B*. Bacillus after six days of treatment with PAS, showing the disintegration of the cytoplasm. (×21,000)

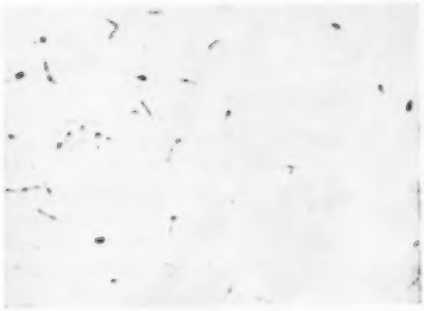

FIG. 3. Phase contrast picture of the bacilli examined after seventy-two and ninety-six hours of treatment with PAS. The bacilli are long and show bulging of the mitochondria at one end. (×1,500)

FIG. 4. The bacilli seen after forty-eight to seventy-two hours of treatment with isoniazid are thick and dense, in which no differentiation of the internal structure may be made. Note one bacillus at one corner with disintegrated cytoplasm. (×21,000)

FIG. 5. Phase contrast picture of the bacilli examined after treatment with isoniazid. The bacilli are thick and dense. (×1,500)

FIG. 6. The bacilli examined after twenty-four hours of treatment with viomycin are long and dense. (×21,000)

FIG. 7. The bacilli examined after seventy-two to ninety-six hours of treatment with viomycin are long and dense with bulging at the end. (×21,000)

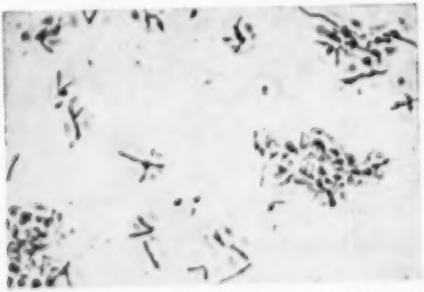

FIG. 8. Phase contrast picture of the bacilli examined after treatment with viomycin. The bacilli are long and dense. (×1,500)

Effect of PAS: There was no appreciable effect on the cytology of the tubercle bacilli after twenty-four hours' treatment with PAS. After forty-eight hours, however, a small number of the bacilli became elongated. The effect was better noticed after seventy-two hours' and ninety-six hours' treatment with the drug. The bacilli seen at this stage were elongated (approximately twice the size of the normal bacilli) with bulging at the end. The electron scattering granules are seen clearly (figures 1*A* and *B*). After seven days the effect was the same except in the case of approximately 1 per cent of the bacilli, which showed disintegration of the cytoplasm (figures 2*A* and *B*). The same results were seen under the phase contrast microscope (figure 3).

Effect of isoniazid: The effect of isoniazid was different from that of PAS. After twenty-four hours' treatment with isoniazid (figure 4), the bacilli appeared thick, dense, and undifferentiated. The same observations were made with the phase contrast microscope (figure 5).

Effect of viomycin: The effect of viomycin was very rapid. After twenty-four hours' treatment with the drug, elongated bacilli were observed which were dense to the electron beam (figure 6). After forty-eight hours and seventy-two hours of treatment, the majority of the elongated bacilli developed swelling at one or both ends (figure 7). No differentiation of the internal structure could be made. There was a slight decrease in the density after seven days.

The same changes were observed under the phase contrast microscope, as will be seen from figure 8.

* * *

The following table summarizes the changes observed in the cytology of tubercle bacilli as a result of action of different drugs. It will be seen that there is a definite variation in the changes produced:

CHANGES IN THE CYTOLOGY OF TUBERCLE BACILLI BY ACTION OF DIFFERENT DRUGS

Drug	Elongation	Swelling	Density	Structural Differentiation	Disintegration
Streptomycin	++	Seen in the middle at first	Slight increase	Remained to fourth day	Marked after fourth day
PAS	++	Seen near the end	Slight increase	Seen throughout	Seen only in about 1% of bacilli after 7 days
Isoniazid	±	Very little	Marked increase	None after 24 hours	Very rare
Viomycin	+	At the end	Marked increase	None after 24 hours	None observed

± Indefinite
\+ Marked
++ Well marked

In summary: The effects of para-aminosalicylic acid (PAS) and viomycin have been studied on a strain of tubercle bacilli of bovine origin. Under the influence of PAS, long

bacilli with bulging at the end are seen. With isoniazid, the bacilli become dense and undifferentiated, whereas viomycin causes elongation with loss of structural clarity.

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Correspondence

FATAL CASE OF TUBERCULOSIS PRODUCED BY BCG

To the Editor of The American Review of Tuberculosis and Pulmonary Diseases:

In the note on a fatal case of tuberculosis produced by BCG, Dr. E. F. James (Am. Rev. Tuberc., 1955, *71*, 321) states that he believes "that BCG is the most dangerous substance which has ever taken shelter behind the principle of protective inoculation." He therefore calls on your National Tuberculosis Association to conduct "an impartial, expert inquiry into the danger of BCG vaccination as there seems to be a more dispassionate attitude in the U.S.A. than in Europe to the vaccination."

As James has addressed his letter to you from a hospital of the Northern Ireland Tuberculosis Authority, it is relevant to inform your readers that BCG vaccination is part of the official medical policy of that Authority, and BCG vaccination is carried on in every county of Northern Ireland so that it is clear that the views expressed by James are not widely held in this country.

In 1949 the American Trudeau Society (Am. Rev. Tuberc., 1949, *60*, 681) published a statement on BCG vaccination of which the first paragraph reads: "BCG vaccine prepared under acceptable conditions, and administered by approved techniques to persons negative to tuberculin, can be considered harmless." It is presumable that this statement was not made without impartial, expert inquiry having been made, and the Society may or may not be inclined to reopen the matter as a result of the further evidence now quoted by James. In assessing the situation it should be remembered that even in medicine hard cases make bad law.

The fatal case reported by Meyer (Am. Rev. Tuberc., 1954, *70*, 402) is fresh in the minds of your readers. There was a widespread malignant tuberculosis involving only the lymphatic system. The tissues did not show tubercle formation anywhere, and Professor Engelbreth-Holm reported that he could not categorize the findings and could not explain the atypical pathologic changes. Meyer concluded that the case was exceptionally rare.

James goes on to quote the fatal cases of tuberculosis following BCG vaccination in Hungary in 1930 described by Irvine (IRVINE, K. N.: BCG Vaccination in Theory and Practice, Blackwell, Oxford, 1949), but he omits to mention that Irvine went to Hungary to investigate these cases and was unable to reach a conclusion about them as "the failure to examine the vaccine or the stock culture, the absence of autopsy in the first and third cases, the inadequate bacteriological investigation of the autopsy material, all render discussion so speculative as to be scientifically useless." It must also be pointed out that Irvine *did not* say that in one of the cases the tubercle bacilli were not pathogenic to guinea pigs. What he said was that inoculation of a subculture of pus from one of the children produced no macroscopical tuberculous lesions in two guinea pigs that were killed and autopsied four weeks later. This negative finding at four weeks after inoculation proves nothing.

In the cases reported from Santiago (*see* Irvine, above) in 1929, when four of ten children vaccinated with BCG at birth developed tuberculous lesions and one of them died of tuberculosis, it was reported that the child who died was being treated for congenital syphilis. He developed varicella at twelve months, and a dense shadow was found in the upper zone of the right lung; the child did not thrive, and he died at the age of two years from bronchopneumonia. At autopsy pulmonary and hilar tuberculosis was

found; the tubercle bacilli grown were equally pathogenic for guinea pigs and rabbits but not for calves. One of the authors of the original report is quoted as considering that the child's resistance to the virulence of BCG had been lowered (by intercurrent disease). Irvine's comment is that "unfortunately so much attention has been concentrated on the possible infectivity of the nurse that the antecedent history of the four children is not recorded, in particular whether they were given BCG because they were in tuberculous surroundings."

The next fatal case quoted by James is that reported by Despierres and Viallier (Rev. de la tuberc., 1951, *15*, 451), the details of which are of interest. A newborn infant was vaccinated with BCG by scarification on the ninth day of life. No contact with a known source of tuberculous infection during the early weeks of life was known. Ten weeks after vaccination the infant had swollen glands on both sides of the neck, in the left supraclavicular fossa, under the left clavicle, and in the left masseter. The glands were incised, and much pus drained which resembled that from a cold abscess. Direct examination of the pus, culture, and inoculation into a rabbit and a guinea pig failed to reveal any microorganism. The child wasted and died three months after vaccination. The authors say they found it very difficult to interpret these findings and continue: "without having absolute proof we hold the conviction that there was a bacillary adenitis whose development was aided—to say the least of it—by the BCG."

It is remarkable that no tubercle bacilli or other microorganisms were found in the above case in spite of the full bacteriological examination described.

The next deaths mentioned by James are those reported by Domingo in 1953 (Rev. mex. de tuberc., 1953, *14*, 129). Dr. Pedro Domingo is Director of the National BCG Institute of Cuba, and he was invited to conduct an investigation into BCG vaccination in Mexico where, as James says, deaths from tuberculosis had occurred in infants previously vaccinated with BCG (90 mg. orally). Infantile morbidity and mortality rates were examined, and it was seen that both rates were much more favourable in the group of infants vaccinated at birth with BCG than in unvaccinated infants. This may have been a reflection of the selection of infants to be vaccinated.

James then turns to the indirect effects of the vaccine which he claims cause death, and his first source of information here is Ustvedt (Conference on European BCG Programmes, International Tuberculosis Campaign, 1950, p. 243), whom he quotes as reporting 21 cases of meningitis and miliary tuberculosis which had developed in vaccinated persons during the BCG campaign of the Joint Enterprise in Europe after the second World War. It is profitable to read Ustvedt's report. He says "The Joint Enterprise was launched by doctors convinced that BCG is generally speaking harmless, and I would like to state at the outset that, in my opinion, no observations published in the literature nor collected during the work of the Joint Enterprise have refuted this basic assumption. This does not exclude however the possibility that application of BCG may in certain circumstances or in exceptional cases do harm to the individual vaccinated."

James says it is not disputed that, "if a person is vaccinated who is incubating a tuberculous infection or who has previously been tuberculin-positive but has lost his skin hypersensitivity, the vaccination may precipitate serious tuberculous disease," but Ustvedt after examining this question at great length in the light of reports in the literature and experience gained in the work of the Joint Enterprise says—"Most of the cases reported have been so incompletely described that they yield little or no information. I am astonished at the ease with which some doctors, even with an academic degree, are drawing conclusions in this very complicated field from very meagre material."

Ustvedt could find very little evidence to indicate that tuberculous disease occurring in individuals vaccinated with BCG in the pre-allergic phase is more serious than when no BCG has been given. As for the harmful effect of BCG on a person who has been tuberculin-positive previously but has lost his skin sensitivity, Ustvedt found the evidence meagre in favour of the hypothesis that BCG might aggravate tuberculous disease in a healthy tuberculin-negative individual but when active tuberculosis is present it can be aggravated by BCG.

The 21 cases of meningitis and miliary tuberculosis which developed in the 6,000,000 persons vaccinated with BCG in the Joint Enterprise campaign in Europe were studied by Ustvedt, and his conclusion after examining all the available evidence is—"No positive evidence has been obtained for the assumption that the BCG vaccination may have contributed to the development of the disease."

The fatal case reported by Wolk (Tuberculosearzt, 1952, *6*, 23) is of great medical interest, and, as it was published in German, some account of it may be permissible here. In March, 1950, a girl aged 14½ years was examined because of menorrhagia. On February 14, 1950, she had had a percutaneous tuberculin test to which she did not react, but it was followed by epistaxis for several days. On February 21 she was Mantoux tested and there was no reaction. This test was also followed by epistaxis for several days. On March 2 she was vaccinated with BCG. On March 13 there was vaginal bleeding which was regarded as her second menstrual period, there having been vaginal bleeding for one day at the beginning of February which was regarded as the menarche. The bleeding was now so continuous that she was confined to bed. She was admitted to the hospital on March 21, having had a rigor.

On examination the girl was seen to be pale and in poor condition. The vaccination site on the leg was normal, and there were no abnormal physical signs anywhere.

The temperature curve was typical of a septic illness, and the clinical appearance also was that of sepsis with severe anaemia. There was no palpable enlargement of the spleen. In the days following, punctate haemorrhages were seen in the skin and the mucous membrane of the mouth. Death occurred on April 7.

The condition was an acute panmyelopathy. This is stated to be usually of toxic, toxic-allergic, or infective origin. In this case the girl had taken no drugs in the month before the onset of the illness nor had she been exposed to any other noxious agent. There was no evidence of infection. The only other factors are the tuberculin tests and BCG vaccination.

Wolk considered that there was a familial weakness of bone marrow and that the BCG vaccine must be blamed for pulling the trigger which precipitated the shock reaction in the bone marrow. He remarks that perhaps such a mishap may be avoided if tuberculin tests are read by experienced physicians who can detect signs of idiosyncrasy in candidates for BCG vaccination. This refers to the fact that the girl had epistaxis after both preliminary tuberculin tests. If indeed this fatal haemorrhagic state was brought about by tuberculin in a person who had no skin sensitivity to it and in whom there is no mention of a Koch phenomenon at the site of vaccination, the event is entitled to be categorized as a medical curiosity. It is not clear to the writer why there is no mention of idiopathic aplastic anaemia as the diagnosis in this case. The history favours it.

The next fatalities mentioned by James as due to BCG vaccination are the cases reported by the late Dorothy Price (Irish J. M. Sc., 1954, *338*, 56). In a follow-up of 104,697 BCG vaccinations in the Republic of Ireland, five deaths from miliary disease or meningitis in BCG-vaccinated persons were reported. The diagnosis was confirmed

only in the second of these cases. The child became ill one month after vaccination, small vaccination lesions were present (4 mm.), and the Mantoux reaction was negative. In the first case of meningitis there were vaccination lesions of average size, and the child was a reactor. The illness occurred three months after vaccination. Both children were in contact with a source of tuberculous infection, and they were not isolated from it. Tubercle bacilli were not found in any of the cases and in the last three the diagnosis was based only on clinical opinion unsupported by radiological or definite bacteriological evidence. In the table presented in the paper it is seen that Price put a question mark before the diagnosis in each case. In these circumstances it is not reasonable for James to speak of "the disease" as though tuberculosis had been proved to exist in these three cases without giving at least some of the qualifying details mentioned in Price's paper.

The last fatal case quoted by James is that of Dufourt and Despierres (Rev. de la tubere., 1951, *15*, 1111), of which he says that "the authors were in no doubt that the vaccination was the precipitating factor in causing death." A child aged fourteen months was vaccinated with BCG by scarification on March 4, 1950, having been found negative to "an organism of antituberculous prophylaxis." (It is not clear what this was.) The test was made eight days before vaccination. Four days after vaccination there was a severe local reaction, and eight days later there were high fever and left hilar adenitis. The skin reaction (to tuberculin) was now ++. The child was admitted to the hospital with signs of meningitis. The cerebrospinal fluid showed 52 leukocytes per cu. mm., 3.5 gm. per 100 ml. of protein, and 0.50 gm. per 100 ml. of sugar. A guinea pig inoculated with the fluid became a reactor at six weeks, and died of tuberculosis at six months. The tubercle bacillus isolated was highly resistant to 50 γ of streptomycin per ml. although the child had not been treated with streptomycin up to the time the cerebrospinal fluid was withdrawn. Death occurred in less than a month.

It seemed that a latent primary infection had been stirred to activity. The child may have been vaccinated during the pre-allergic phase or at the height of the infection because of faulty tuberculin testing. The Koch phenomenon and the appearance of tuberculin sensitivity eight days after vaccination show that the child was already infected before vaccination. "It is possible that even in the absence of vaccination both hilar adenopathy and meningitis would have declared themselves at the same time but their rapid succession suggests cause and effect." This is what James calls being in no doubt!

No information is available in the paper about the pre-vaccinal test in this case, nor about any care taken to segregate the child from a source of infection, nor whether the source was in fact discovered. It is notorious that serious forms of tuberculosis are common in children infected at the early age of this child (under 14 months), and it cannot be lightly assumed that the child would not have been ill had he not been vaccinated. Such an assumption however presents no difficulty to James.

In the above review I have not introduced any witnesses that were not called by James. I have however examined them somewhat more fully than he appears to have done. If the National Tuberculosis Association is disposed to listen to James's call to the New World to redress the balance of the Old, some of the facts I have presented may be of assistance to them. I feel, however, that the 1949 statement of the American Trudeau Society quoted at the beginning is still in accord with informed American opinion. The subject should however be kept always under review as there are constant opportunities for spontaneous mutation with a living organism. This possibility is well in the minds of the bacteriologists who test the strains of BCG for virulence on the one hand and immunizing power on the other. Adequate pathological and bacteriological

investigations must be made in any case in which lesions arise which might be attributed to BCG, but in considering these it is essential to pay attention to *all* the relevant facts and the opinions of the investigators.

9 Marine Parade
Whitehead
Belfast
Northern Ireland

H. G. Calwell

May 18, 1955

ANTIMICROBIAL TREATMENT OF PRIMARY TUBERCULOUS INFECTION IN CHILDREN

To The Editor of The American Review of Tuberculosis and Pulmonary Diseases:

In my letter on "The Problem of the Antimicrobial Treatment of Primary Tuberculous Infection in Children" published in the September issue of the American Review of Tuberculosis and Pulmonary Diseases, I stated (p. 400) "Others advocate a thorough treatment for every recent tuberculin converter irrespective of age" and I gave as the reference for this statement Dr. James J. Waring's article in the *Diseases of the Chest* (1954, *25*, 361). Dr. Waring has kindly pointed out to me that he limits his recommendations for antimicrobial treatment to recent converters *among highly exposed persons* and that at the moment he does not recommend antimicrobial treatment for *all* recent tuberculin converters.

I very much regret if inadvertently I gave some of your readers an erroneous picture of Dr. Waring's views on this important subject.

Yours sincerely,

Department of Health
Ontario
Canada

Stefan Grzybowski

September 22, 1955

Books

THE BIOLOGIC EFFECTS OF TOBACCO: Edited by Ernest L. Wynder. Pp. 215, Little, Brown and Company, Boston, Massachusetts, 1955, Price $4.50.

The editor of this book has undertaken to review the scientific information about tobacco in relation to man's health. He has been aided by seven collaborators, and has divided the subject into the following sections: two chapters on the chemistry and pharmacology of tobacco and tobacco smoke; four which deal with the relationship between smoking and the cardiovascular system, neoplastic diseases, the gastrointestinal tract, and allergy, respectively; and a final section entitled "Cause and Effect" which considers the kind of evidence necessary to establish a causal relationship between smoking and disease. A large number of references are cited.

From the beginning one becomes aware of how much the work on this subject has suffered from lack of care, precision, and standardized conditions of study, and this opinion is strengthened in the sections on pharmacology, cardiovascular effects, gastrointestinal effects, and allergy. Conflicting findings are rife in the literature. Much of the confusion seems to be due to the complex and variable nature of tobacco smoke, and much to the inconsistency in the physiological effects of smoking, depending on dosage, time, habituation, physiological state, and other variables which in many studies have been poorly controlled. Many of the cited studies were poorly designed, with too few subjects, improper or no controls, or reliance on clinical "before and after" observations. The whole subject of the pharmacological effects of smoking needs restudy and it may be hoped that this book will stimulate further work.

The following statements taken from the summary of the chapter on the gastrointestinal tract seem applicable to other phases of the problem as well: "This review indicates only that our knowledge of the influence of use of tobacco upon the gastrointestinal tract is fragmentary. . . .Insufficient recognition of all the possible variables which may play a role in the effects has not been fully appreciated."

The chapter on allergy, in which the literature is critically appraised, is very well written. The author concludes that, aside from the uncommon or rare cases of allergic dermatitis or asthma, the case for allergic responses to tobacco as a cause of clinical disease is unproved.

The question of the relationship between smoking and lung cancer is dealt with by the editor in the chapter on neoplastic diseases and again, more generally, in the final chapter by Hammond. Since both authors, on the basis of their own investigations, have become strong proponents of the view that smoking is a causative factor in lung cancer, they could not perhaps avoid presenting a somewhat partisan picture. This is especially true of Wynder's chapter. The most effective review of this controversial subject might perhaps be made by someone who had not himself worked on it, and who could preserve a more detached and judicial attitude. It might be difficult to find such a person; the writer acknowledges that he has for some time been strongly impressed by the evidence.

The chapter entitled "Cause and Effect" is an excellent summary of the epidemiologic method as applied to chronic disease, the pitfalls and advantages of various approaches, and the logical grounds for proceeding to a hypothesis of causation once association has been determined.

The diseases with which tobacco smoking is most clearly correlated are thromboangiitis obliterans and epidermoid carcinoma of the lung. In certain established diseases of the cardiovascular system, and of the stomach and duodenum, the use of tobacco is said to influence unfavorably the clinical course. Beyond these two statements, one is on shaky ground in respect to a relationship between chronic disease and tobacco at the present time.

Despite its limitations and imperfections, this book will be of considerable value. It brings together many references to published work, indicates what has been clearly established and, perhaps even more important, calls attention to many areas where more and better work must be done.

PHILIP E. SARTWELL
Baltimore, Maryland

ANTIBIOTICS AND ANTIBIOTIC THERAPY: A Clinical Manual. By Allen E. Hussar and Howard L. Holley. Cloth Pp. 475, The Macmillan Company, New York, New York, 1954, Price $6.00.

This primer is concerned with the use of currently available antibiotics. In the first section the fundamentals of chemotherapy are discussed, and the authors present what they recommend as acceptable chemotherapeutic procedure in the form of "12 Commandments." The second section of the book is a discussion of the chemical and clinical pharmacologic behavior and antimicrobial effects of these drugs in the several dosage forms now available. The third and final section of this book comprises the major portion, and is entitled "The Drug of Choice." The publishers represent this book as the first clinical manual on the properties, potentialities, and limitations of the antibiotics in clinical practice.

There are at least two general medical and several other specialized medical and therapeutic texts, as well as numerous articles and editorials, all recently published, which have served to establish a high standard in the organization of current knowledge in this field. Therefore, this new book has been read by the reviewer with particular attention to the question, "Are the contents or approach of this book new or more serviceable than the contents or approach of current publications which are widely distributed?" The book does not compare favorably with publications already available. There are errors in the text; the streptomycins are characterized as the drug of choice in the treatment of tuberculosis; the authors recommend that procaine penicillin be used in the treatment of *Staphylococcus* and *Streptococcus viridans* infections. Treatment schedules are complicated and antimicrobials are recommended uncritically; different treatments are advocated for severe and mild infections caused by a given microorganism; the use of antimicrobials in the vast majority of viral infections is justified on the premise that secondary bacterial invasion usually follows viral infections. The book is too long; the third section includes a forty-page discussion of the treatment of viral, fungal, and parasitic infections. Antimicrobials are of limited value in these infections. This section could have been stated more briefly. The third section also includes over seventy-five pages of discussion of infections encountered in pediatrics, dermatology, and the various surgical specialties. This material is essentially a review and merely states what has been already discussed in the foregoing text. Apparently the book has not been carefully edited for there are errors in sentence structure as well as textual ambiguities. These defects

are not counterbalanced by the praiseworthy and practicable organization, the generally adequate bibliographies, and the clear, large type of the book.

CARL BERNTSEN, JR.
New York, New York

WISH I MIGHT. By Isabel Smith. Pp. 234, Harper & Brothers, New York, New York, 1955, Price, $3.00.

This book is a personal account of the author's treatment for tuberculosis over the past twenty-five years. In a preface to the book, Dr. Francis B. Trudeau sums it up, "Having been under treatment for over a quarter of a century, she has had personal experience with the three phases of tuberculosis therapy which have been developed during this period."

Medically speaking, the book presents nothing new for physicians. It is, however, interesting and valuable to the profession because it expresses the patient's viewpoint, and explains the treatment of tuberculosis in terms that the average reader will understand and enjoy. It is possibly fortunate for those concerned that her angle of approach was, "The book would give me a chance to say 'thank you' for all the wonderful things that have happened to me since I came to Saranac Lake." In doing this, she avoids many adverse comments frequently made by other patients.

The discouraging picture of a twenty-five-year cure is relieved by Miss Smith's lively adjustment to her illness and in the end of the book, by her romance, marriage, and her ability to assume a reasonably normal life. She effectively points out the tendency of the patient to center all thoughts on himself so that the walls of the room or porch become the outer boundaries of existence. She stresses also the value of rehabilitating the chronically ill in measured doses from the beginning of a long illness.

This book is, in a manner, a history of a sanatorium now closed, a form of treatment now abandoned, and of a relapsing course of disease which we will probably rarely again see.

The story shows repeatedly how the casual word or action of the physician may aid or adversely affect the patient far out of proportion to any intended effect.

The book is also a tribute to the Trudeau Sanatorium because this is where the story is laid. Miss Smith's gratitude to the Sanatorium, to Dr. Francis Trudeau, and to many members of the staff makes an enduring picture of Trudeau Sanatorium that will last long in the minds of the readers of this book.

The entire effect of the book is encouraging and positive. It is an excellent study of the difficulties to be combatted in the treatment of any patient with a long, relapsing chronic disease.

R. L. YEAGER
Pomona, New York

BOOKS RECEIVED

THE CHANGING CHARACTER OF TUBERCULOSIS. By Joint Tuberculosis Council. Pp. 28, Joint Tuberculosis Council, Bovey Tracey, Devon, England, 1955, Price, 1s.

LA LÈPRE. 2nd Edition. By R. Chaussinand. Pp. 312, Expansion Scientifique Française, Paris, 1955, Price, 3,800 fr.

DRIED BCG VACCINE. By Yoji Obayashi. Pp. 220, World Health Organization, Geneva, 1955, Price, $5.00.

A ESPELEOSTOMIA DE BERNOU. By Fernando Rodrigues. Pp. 111, Gazeta Médica Portuguesa, Lisbon, 1954–1955.

Studio Anatomo-Radiologico sui Processi di Regressione Della Tubercolosi Polmonare in Trattamento Chemio-Antibiotico. By Gaetano Tricomi and Antonio Perelli. Pp. 127, Emes, Rome, 1955.

A Study of Patients' Attitudes Toward Care at Firland Sanatorium. By Catherine Vavra and Edith Dyer Rainboth. Pp. 181, Firland Sanatorium and Department of Public Health and Preventive Medicine, The School of Medicine, University of Washington, Seattle, Washington, 1955, Price, $2.00.

The Life of Bacteria. By Kenneth V. Thimann. Pp. 775, The Macmillan Company, New York, New York, 1955, Price, $13.50.

Pathology Seminars. Edited by Robert S. Haukohl and W. A. D. Anderson. Pp. 195, The C. V. Mosby Company, St. Louis, Missouri, 1955, Price, $10.00.

Obituaries

DAVID W. HEUSINKVELD

1897–1955

Dr. David W. Heusinkveld was born on July 17, 1897, in Fulton, Illinois. His father was Henry J. Heusinkveld, M.D. (University of Michigan Medical College, 1883) and his mother was Alice Munneke Heusinkveld, schoolteacher. All four grandparents were born and reared in The Netherlands. He was sixth in a family of ten children, eight boys and two girls, seven of whom are still living. One brother is a practicing physician in Clinton, Iowa.

Dr. Heusinkveld attended Hope College, Holland, Michigan, and while in attendance there had military training S.A.T.C. at Ft. Sheridan. Being commissioned 2nd Lieutenant, Infantry, he was assigned to duty at the University of Cincinnati. After his wartime experience, he entered the University of Chicago, receiving a B.S. in 1921. He then attended Rush Medical College, from which he was graduated in 1924. His education at Rush was interrupted after the junior year for one year to fill a research appointment in pharmacology at the University of Wisconsin, where he studied trypanosomiasis in white rabbits and syphilis in rats. After graduation from Rush he came to Cincinnati for a rotating internship at Cincinnati General Hospital.

Following his hospital training, Dr. Heusinkveld became associated in the practice of internal medicine with Dr. Kennon Dunham and Dr. John H. Skavlem. Later this group became Drs. Skavlem, Heusinkveld, and Plessinger. In 1934 he was appointed instructor in the faculty of the College of Medicine, University of Cincinnati, and later became Assistant Clinical Professor of Medicine. He was attending physician in medicine at Good Samaritan, Bethesda, and Dunham hospitals.

In 1939 Dr. Heusinkveld was elected to the Board of the Cincinnati Anti-Tuberculosis League, and served this organization in various capacities from that time until his death, when he was Chairman of the Christmas Seal Committee (a post he held for eight years), a member of the Executive and Finance committees and of the Medical and Program committees. He was president of the Anti-Tuberculosis League for three years, 1945–1948. In 1941 he went to New York City to study methods of case reporting from clinical records. As a result of this study, the Anti-Tuberculosis League purchased for the City Health Department a photo-roentgenogram unit for 4- by 5-inch film. In 1944 the Anti-Tuberculosis League initiated its industrial health program under Dr. Heusinkveld's leadership. The first mass chest survey roentgenograms were done through this program.

Dr. Heusinkveld was a Fellow of the American College of Chest Physicians and served that organization as Ohio Governor since 1950. He was a charter member of the Ohio Trudeau Society and served as President of the Ohio Tuberculosis Association from 1953 through 1954. He had been a member of the National Tuberculosis Association and of the American Trudeau Society since 1940.

Dr. Heusinkveld served as President of the Hamilton County Medical Society in 1948–1949. He served for one term (1950–1952) on the Board of Directors of the Cincinnati Chamber of Commerce. In 1949 Dr. Heusinkveld was appointed to the Board of Trustees of the Hospital Care Corporation for Southwestern Ohio, representing the

medical profession. He was elected Vice-President in 1950 and President in 1952, serving two years in that office. He was a member of the original Medical Advisory Committee from its inception in 1949 to the time of his death and served on the Executive Committee from 1950. For five years Dr. Heusinkveld served as a member of the Council of the Ohio State Medical Association representing the First District. He was named President-Elect at the annual meeting in 1954, and took office as President April 22, 1955, when the convention was held in Cincinnati.

Dr. Heusinkveld became a member of the Mt. Auburn Presbyterian Church soon after coming to Cincinnati and maintained active membership in the same church until the time of his death. He was elected to the Board of Elders in 1946.

In addition to his widow, Dr. Heusinkveld is survived by two sons, Dr. David W. Heusinkveld, Jr., of Salt Lake City, Utah, and Kennon D. Heusinkveld of New York City.

Dr. Heusinkveld died suddenly and entirely unexpectedly of coronary thrombosis on June 25, 1955, in Columbus, Ohio, while in attendance there as President of the Ohio State Medical Association. He died at the height of accomplishments and recognitions, respected and beloved by family, colleagues, patients, and friends. He possessed an innate talent in the art of medicine, expressed particularly by his ability to care for patients in bed for long periods of time and keep them happy. For the present writer a happy association with deep respect of twenty-eight years in medical practice is broken.

J. H. S.

HENRY A. RANDEL

1902–1955

Dr. Henry A. Randel of Fresno, California, died at Morro Bay on August 19, 1955, of a cerebral vascular accident.

Dr. Randel was a graduate of Northwestern University Medical School and was certified by the American Board of Internal Medicine. He was a member of the staffs of three hospitals in Fresno.

Dr. Randel had long been interested in tuberculosis and had done a great deal of work in this field in his section of the state. He was also active in the California Medical Association. He served for twenty-five years as a director of the Fresno County Tuberculosis Association and had been President of that group. He had been a member of the Fresno County Heart Association, the Fresno County Medical Society, and the California Trudeau Society. During the last year he was Chairman of the California Medical Association Council on rural health. He was a Fellow of the American College of Chest Physicians.

Dr. Randel is survived by his wife, Christine, two daughters, a sister, and four grandchildren.

W. H. O.

EUGENE B. PIERCE

1875–1955

Dr. Eugene B. Pierce of Hudson, Ohio, suffered a stroke on August 8 and died on August 29. He was eighty years old.

Dr. Pierce studied at the University of Michigan to become a medical missionary, but an attack of tuberculosis changed the course of his life. From 1909 to 1925 he was superintendent of the Michigan State Sanatorium at Howell, leaving there in April, 1925, to work with the Department of Public Health at Flint. In 1930 he became superintendent

of the Molly Stark Tri-County Sanatorium at Canton, Ohio, where he remained until he retired at the age of seventy.

Dr. Pierce was a member of the Livingston County Medical Association, Mississippi Valley Tuberculosis Association, the Michigan Tuberculosis Association, the National Tuberculosis Association, the American Trudeau Society, and the Michigan Trudeau Society. He leaves his wife, two daughters, and a son.

H. R. G.

FRED GOODING HOLMES

1889–1955

Fred Gooding Holmes, who was born in 1889, led a wonderfully versatile and productive life, including the last thirty-five years spent in Arizona, until his sudden and tragic death on August 6, 1955. A boat containing his son and two grandsons and himself overturned in the Klamath Bay, and all were lost.

Fred Holmes early learned the need for hard work, and during the time when he earned his way through college at the University of California he helped support his mother, brothers, and sisters. He continued with this energy and self-discipline the remainder of his life. He graduated from Harvard Medical School in time to serve in the first World War and immediately thereafter started general practice in Phoenix, Arizona.

The superior knowledge of a colleague concerning chest diseases challenged him to obtain special information, and he went to the Trudeau School of Tuberculosis in 1920. He experimented and published articles on the use of pneumothorax and soon became a local authority.

In 1935 he was found to have tuberculosis, and during nine months of bed rest he wrote a popular book on the subject for the use of patients, publishing it at his own expense.

During the course of his years in Phoenix he became certified in the American Board of Internal Medicine and as a specialist in pulmonary diseases. He was a member of the American Trudeau Society, the American College of Chest Physicians, and the American College of Physicians.

He had diverse interests, into which he entered with a tremendous drive and persistence. He worked for the Y.M.C.A., and helped raise large sums of money for their building. He worked for the Presbyterian Church, and helped obtain a revision of the creed. He became a member of the National Board of the church. He entered politics, but limited his chance of election by taking an unpopular stand on fair employment practices. Later on he entered the field as a strong opponent of discrimination against minority groups and, because of his efforts in Arizona on desegregation in the schools, he is given credit for influencing the later decisions of higher courts.

His loss has been a serious one to Phoenix and to medicine in Arizona, and is most likely to be felt in wider spheres.

W. O.

NOTICES

ANNUAL MEETING

The Fifty-First Annual Meeting of the American Trudeau Society will be held in New York, New York, beginning on Monday, May 21. The meeting is in conjunction with the joint Annual Meetings of the National Tuberculosis Association and the National Conference of Tuberculosis Workers.

All program sessions will be held in the Hotel Statler. This will be the headquarters hotel. The October issue of the NTA *Bulletin* contains a list of the cooperating hotels. Also included in the *Bulletin* is the registration form which must be used to obtain reservations at the hotel of your choice.

THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES urges you to send in your reservations early. Additional copies of the registration form may be obtained from the NTA, 1790 Broadway, New York 19, New York.

* * *

There are many scientific sessions planned by the Medical Sessions Subcommittee for Monday, Tuesday, and Wednesday, May 21, 22 and 23. The program for Thursday, May 24, has been planned for the combined interest of medical as well as non-medical persons attending the meeting. The preliminary program, containing subjects and speakers, will be published in the March issue of the *Bulletin*.

GRADUATE STUDIES AT UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE

The College of Medicine of the University of Florida offers opportunities for graduate study in the basic medical sciences in the following fields: Anatomy, Biochemistry, Microbiology, Pathology, Pharmacology, and Physiology.

Applications must be filed not later than March 1, 1956. For further information and necessary forms write to: Office of the Dean, College of Medicine, University of Florida, Gainesville, Florida.

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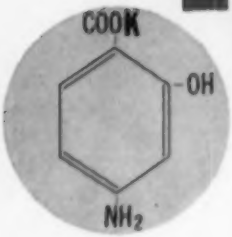

A BETTER FORM OF P.A.S. FOR TREATING TUBERCULOSIS

BETTER TOLERATED

PASkalium largely avoids the common gastrointestinal upsets which limit the usefulness of para-aminosalicylic acid as well as its sodium and calcium salts. Patients with positive histories of intolerance to all previous P.A.S. therapy readily tolerate full therapeutic dosage of PASkalium in most instances.[1]

HIGHER P.A.S. PLASMA LEVELS

PASkalium is the most soluble P.A.S. salt known. Absorption is rapid and excretion predictable. Twelve grams daily produce and maintain blood levels comparable to those obtained with 17 grams of sodium P.A.S. and (theoretically) 30 grams of P.A.S. Acid.[2]

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1. *Molthan, L., Cohen, R. V., and Zarafonetis, C. J. D.: Clinical use of potassium para-aminosalicylate (KPAS). Am. Rev. of Tuberc. and Pulmon. Dis. 71:220 (Feb.) 1955.*

2. *Cohen, R. V., Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations). Read before the American Trudeau Society, Annual Meeting, Milwaukee, Wisconsin, May 23-27, 1955.*

NOW AVAILABLE *in tablets (0.5 Gm.), powder, and convenient one-dose (3 Gm.) "Envules". For information, please write*

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DIRECT X-RAY QUALITY in 4″x4″

photofluorography

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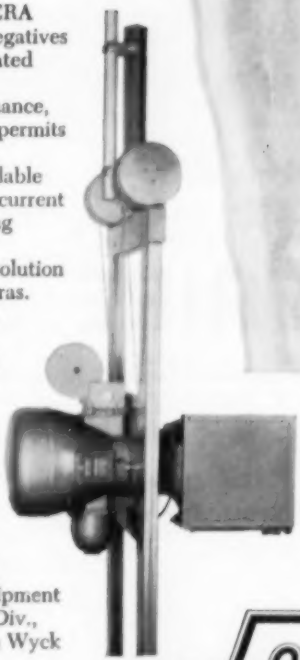

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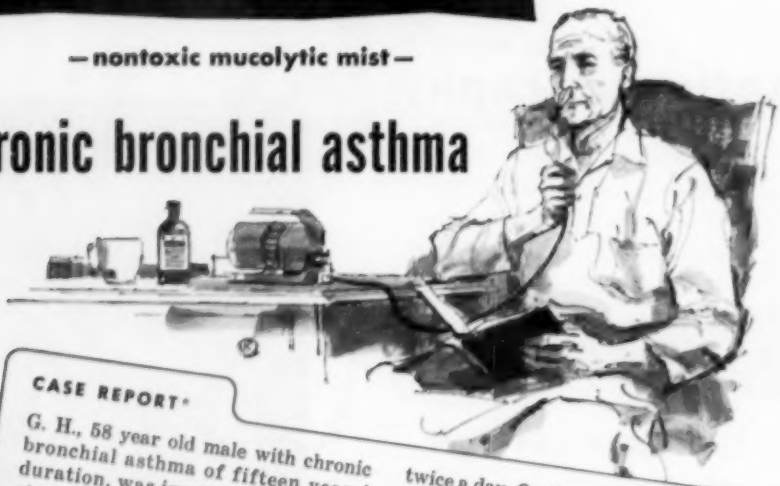
—nontoxic mucolytic mist—

chronic bronchial asthma



CASE REPORT*

G. H., 58 year old male with chronic bronchial asthma of fifteen years' duration, was in moderately severe status asthmaticus. He wheezed constantly and had a persistent nonproductive cough. Occasionally he was able to raise thick, sticky, yellowish sputum. He had to sleep on three pillows, required sedatives each night to sleep, and had to arise for an hour or two nightly to "catch his breath." Expectorant cough syrups, antibiotics, bronchodilators and sedatives had been used without appreciable benefit.

Treatment was begun with Alevaire by direct application of the nebulizer to the external nares for one hour twice a day. On the second day sputum was more liquid and easier to raise; coughing was less frequent and less severe, and breathing became deeper, "quicker" and easier. Bronchospasm and wheezing began to decrease. Patient felt that breathing was more natural and that he could get the air down further into his chest. In fourteen days the wheeze or cough disappeared.

The patient continued to use Alevaire for a short period each night before retiring. He soon required no pillows, had no dyspnea, slept all night without sedation, and rarely was bothered by wheezing.

*Miller, J. B., et al.: *Ann. Allergy*, 12:611, Sept.-Oct., 1954.

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has been dramatically effective in:

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- croup • laryngitis • tracheobronchitis
- pertussis • pneumonia • bronchial asthma
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- poliomyelitis (respiratory complications)
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Alevaire is supplied in bottles of 60 cc. for intermittent therapy and in bottles of 500 cc. for continuous inhalation therapy.

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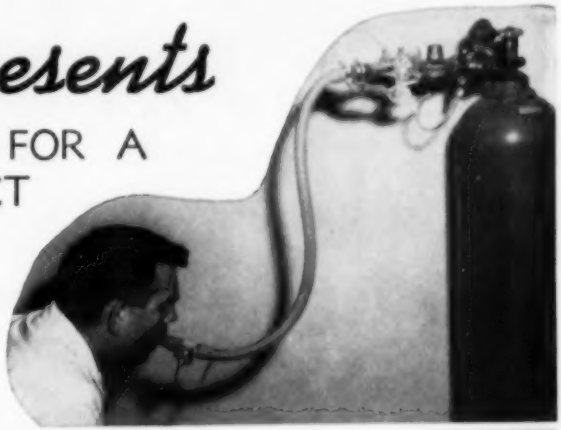

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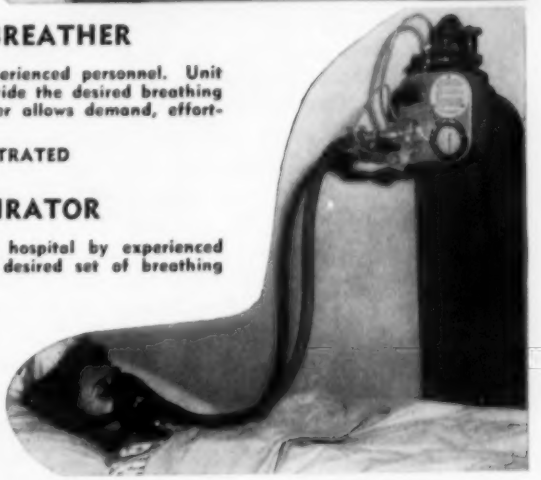

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Both units employ the elements of the Halliburton Respirator

- Provides effortless deep breathing of oxygen and aerosol for the treatment of respiratory disorders, anoxia, respiratory acidosis, atelectasis, cardiac failure, pulmonary edema, and respiratory failure.
- An ideal respirator for open chest surgery and the recovery room.
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1. Hyman, S., and Rosenblum, S. H.: Illinois M. J. 104:257, 1953.
2. Piper, C. E., and Nicklas, F. W.: Industr. Med. 23:510, 1954.

*U.S. Pat. 2,630,400
†U.S. Pat. 2,628,185

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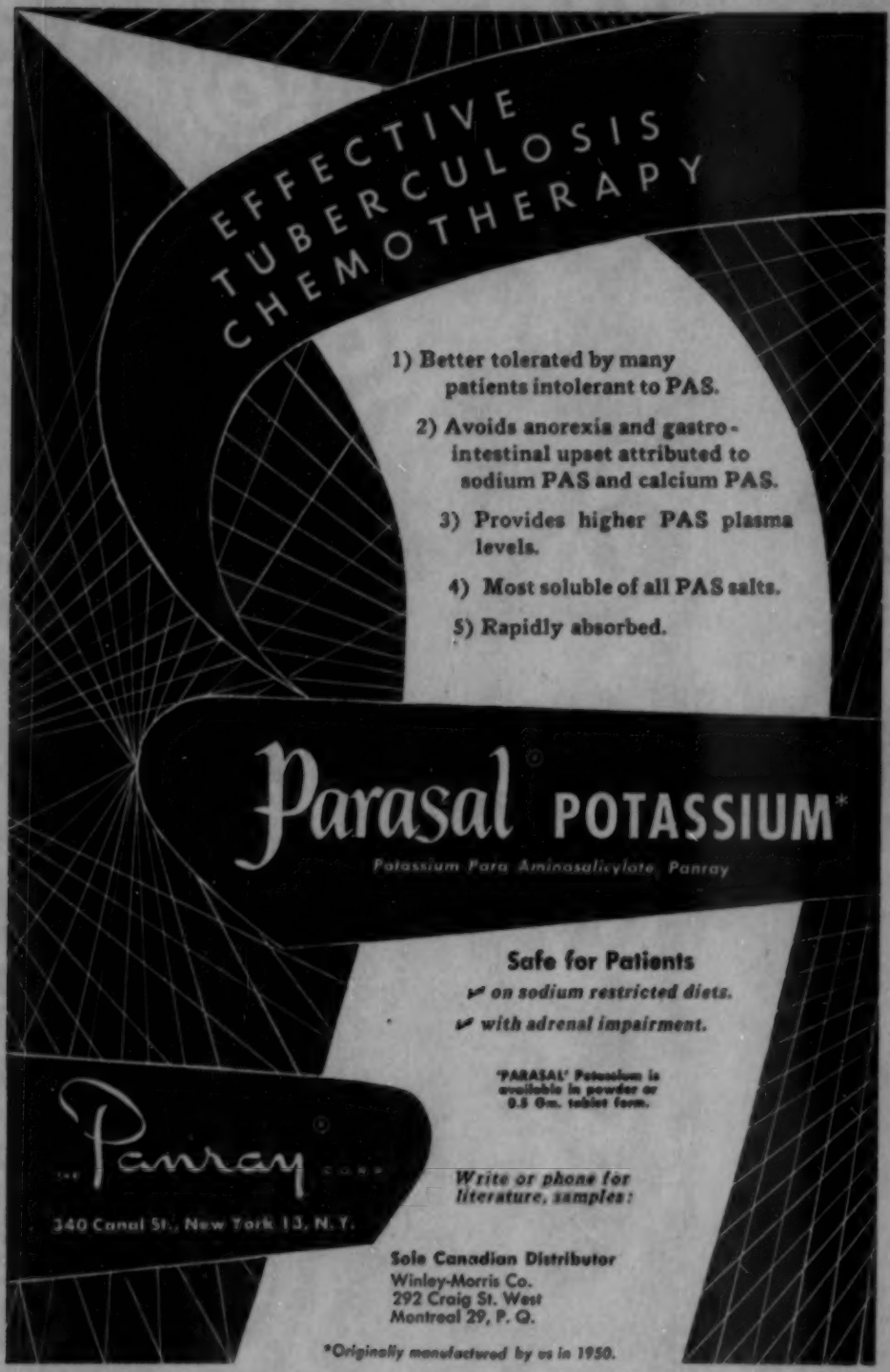
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